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Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs (Review)

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TABLE OF CONTENTS

[Intervention Review]

Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs

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ABSTRACT

Background

Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs

Needle syringe programmes (NSP) and opioid substitution therapy (OST) are the primary interventions to reduce hepatitis C (HCV) transmission in people who inject drugs. There is good evidence for the effectiveness of NSP and OST in reducing injecting risk behaviour and increasing evidence for the effectiveness of OST and NSP in reducing HIV acquisition risk, but the evidence on the effectiveness of NSP and OST for preventing HCV acquisition is weak.

Objectives

To assess the effects of needle syringe programmes and opioid substitution therapy, alone or in combination, for preventing acquisition of HCV in people who inject drugs.

Search methods

We searched the Cochrane Drug and Alcohol Register, CENTRAL, the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA), the NHS Economic Evaluation Database (NHSEED), MEDLINE, Embase, PsycINFO, Global Health, CINAHL, and the Web of Science up to 16 November 2015. We updated this search in March 2017, but we have not incorporated these results into the review yet. Where observational studies did not report any outcome measure, we asked authors to provide unpublished data. We searched publications of key international agencies and conference abstracts. We reviewed reference lists of all included articles and topic-related systematic reviews for eligible papers.

Selection criteria

We included prospective and retrospective cohort studies, cross-sectional surveys, case-control studies and randomised controlled trials that measured exposure to NSP and/or OST against no intervention or a reduced exposure and reported HCV incidence as an outcome in people who inject drugs. We defined interventions as current OST (within previous 6 months), lifetime use of OST and high NSP coverage (regular attendance at an NSP or all injections covered by a new needle/syringe) or low NSP coverage (irregular attendance at an NSP or less than 100% of injections covered by a new needle/syringe) compared with no intervention or reduced exposure.

Data collection and analysis

We followed the standard Cochrane methodological procedures incorporating new methods for classifying risk of bias for observational studies. We described study methods against the following 'Risk of bias' domains: confounding, selection bias, measurement of interventions, departures from intervention, missing data, measurement of outcomes, selection of reported results; and we assigned a judgment (low, moderate, serious, critical, unclear) for each criterion.

Main results

We identified 28 studies (21 published, 7 unpublished): 13 from North America, 5 from the UK, 4 from continental Europe, 5 from Australia and 1 from China, comprising 1817 incident HCV infections and 8806.95 person-years of follow-up. HCV incidence ranged from 0.09 cases to 42 cases per 100 person-years across the studies. We judged only two studies to be at moderate overall risk of bias, while 17 were at serious risk and 7 were at critical risk; for two unpublished datasets there was insufficient information to assess bias. As none of the intervention effects were generated from RCT evidence, we typically categorised quality as low. We found evidence that current OST reduces the risk of HCV acquisition by 50% (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.40 to 0.63, I^2 = 0%, 12 studies across all regions, N = 6361), but the quality of the evidence was low. The intervention effect remained significant in sensitivity analyses that excluded unpublished datasets and papers judged to be at critical risk of bias. We found evidence of differential impact by proportion of female participants in the sample, but not geographical region of study, the main drug used, or history of homelessness or imprisonment among study samples.

Overall, we found very low-quality evidence that high NSP coverage did not reduce risk of HCV acquisition (RR 0.79, 95% CI 0.39 to 1.61) with high heterogeneity (I^2 = 77%) based on five studies from North America and Europe involving 3530 participants. After stratification by region, high NSP coverage in Europe was associated with a 76% reduction in HCV acquisition risk (RR 0.24, 95% CI 0.09 to 0.62) with less heterogeneity (I^2 =0%). We found low-quality evidence of the impact of combined high coverage of NSP and OST, from three studies involving 3241 participants, resulting in a 74% reduction in the risk of HCV acquisition (RR 0.26 95% CI 0.07 to 0.89).

Authors' conclusions

OST is associated with a reduction in the risk of HCV acquisition, which is strengthened in studies that assess the combination of OST and NSP. There was greater heterogeneity between studies and weaker evidence for the impact of NSP on HCV acquisition. High NSP coverage was associated with a reduction in the risk of HCV acquisition in studies in Europe.

PLAIN LANGUAGE SUMMARY

Interventions for reducing hepatitis C infection in people who inject drugs

Review question

We examine research on the effect of needle syringe programmes (NSP) and opioid substitution treatment (OST) in reducing the risk of becoming infected with the hepatitis C virus.

Background

There are around 114.9 million people living with hepatitis C and 3 to 4 million people newly infected each year. The main risk for becoming infected is sharing used needles/syringes. Almost half the people who inject drugs have hepatitis C. The provision of sterile injecting equipment through NSPs reduces the need for sharing equipment when preparing and injecting drugs. OST is taken orally and reduces frequency of injection and unsafe injecting practices. We examined whether NSP and OST, provided alone or together, are effective in reducing the chances of becoming infected with hepatitis C in people who inject drugs.

Search date

The evidence is current to November 2015.

Study characteristics

We identified 28 research studies across Europe, Australia, North America and China. On average across the studies, the rate of new hepatitis C infections per year was 19.0 for every 100 people. Data from 11,070 people who inject drugs who were not infected with hepatitis C at the start of the study were combined in the analysis. Of the sample, 32% were female, 50% injected opioids, 51% injected daily, and 40% had been homeless. Our study was funded by the National Institute of Health Research's (NIHR) Public Health Research Programme, the Health

Protection Research Unit in Evaluation of Interventions, and the European Commission Drug Prevention and Information Programme (DIPP), Treatment as Prevention in Europe: Model Projections.

Key results

Current use of OST (defined as use at the time of survey or within the previous six months) may reduce risk of acquiring hepatitis C by 50%. We are uncertain whether high coverage NSP (defined as regular attendance at an NSP or all injections being covered by a new needle/syringe) reduces the risk of becoming infected with hepatitis C across all studies globally, but there was some evidence from studies in Europe that high NSP coverage may reduce the risk of hepatitis C infection by 76%. The combined use of high coverage NSP with OST may reduce risk of hepatitis C infection by 74%.

Quality of the evidence

Quality of evidence ranged from moderate to very low because none of the studies used the gold standard design of randomised controlled trials.

Summary of findings for the main comparison. Current OST versus no OST for people who inject drugs

Current OST versus no OST

Patient or population: people who inject drugs
Settings: outpatient
Intervention: current OST versus no OST

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No OST	Current OST			
HCV incidence adjusted analyses number of HCV seroconversion Follow-up: mean 440.5 person-years	—	—	**RR 0.50** (0.40 to 0.63)	6361 (12 studies)	⊕⊕⊝⊝ **Low** [a,b]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OST**: opioid substitution therapy; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to overall moderate risk of bias in 2 studies, overall serious risk of bias in 6 studies, 2 studies at overall critical risk of bias in 2 studies; not enough information to make judgment in 2 studies.
[b]Upgraded one level due to large magnitude of the effect: RR: 0.5.

Summary of findings 2. High NSP coverage versus no/low NSP coverage for people who inject drugs

High NSP coverage versus no/low NSP coverage

Patient or population: people who inject drugs
Settings: outpatients
Intervention: high NSP coverage versus no/low NSP coverage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No/low NSP coverage	High NSP coverage			
HCV incidence adjusted analyses number of HCV seroconversion Follow-up: mean 269 person-years	—	—	**RR: 0.79** (0.39 to 1.61)	3530 (5 studies)	⊕⊝⊝⊝ **Very low** [a,b]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NSP**: needle syringe programmes; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to serious overall risk of bias in all the studies.
[b]Downgraded one level due to significant heterogeneity: I^2: 77%.

Summary of findings 3. Combined OST and high NSP versus no OST and low/no NSP for people who inject drugs

Combined OST and highNSP versus no OST and low/no NSP

Patient or population: people who inject drugs
Settings: outpatients
Intervention: Combined OST and high/low NSP versus no OST and low/no NSP

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No OST and low/no NSP	Combined OST and high NSP			
HCV incidence adjusted analyses number of HCV seroconversions Follow-up: mean 356 person-years	—	—	**RR: 0.26** (0.07 to 0.89)	3241 (3 studies)	⊕⊕⊕⊝ Low[a,b]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NSP**: needle syringe programmes; **OST**: opioid substitution therapy; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to serious overall risk of bias in all studies.
[b]Upgraded one level due to very large magnitude of the effect: RR: 0.26.

BACKGROUND

Description of the condition

The number of people exposed to hepatitis C continues to increase globally, with an estimated 114.9 million people living with antibodies to hepatitis C (Gower 2014), 3 to 4 million people newly infected each year and 350,000 deaths occurring annually (Mohd Hanafiah 2013; Perz 2006). There were an estimated 35 million people living with human immunodeficiency virus (HIV) in 2014. Emerging evidence suggests that HIV transmission has declined since 2001 and more people are receiving treatment (UNAIDS 2014). Co-infection with hepatitis C (HCV) among people living with HIV is a major global public health concern, with an estimated 4 million co-infected people (Platt 2016). Among people who inject drugs (PWID), sharing needle/syringes is the main risk factor for infection with HIV and HCV. Additional risks for HCV acquisition in this population include sharing drug preparation containers, filters, rinse water and backloading (a method of sharing drugs by transferring them from the needle of one syringe into the barrel of another) (Pouget 2012; Strathdee 2010).

Description of the intervention

NSPs are often a first point of contact with health services for PWID. They provide support to minimise drug and sexual risk-related harms, including the provision of clean needles/syringes and condoms so as to prevent bloodborne virus transmission, bacterial infections and other adverse health outcomes. By maximising the amount of clean injecting equipment in circulation, it is possible to minimise the time that contaminated equipment remains in use and the proportion of unsafe injections (Bluthenthal 2007; Kaplan 1992). NSPs operate through a range of modalities including via fixed sites, outreach, peer PWID networks, vending machines and pharmacies. Engaging in behaviours that are socially stigmatised and illegal, PWID often have high rates of unemployment, homelessness and incarceration. NSPs also provide access to longer-term support by referring clients to medical, drug treatment or social support services.

Drug treatment for opioid addiction and dependence also encompasses a range of strategies to manage injecting drug use and reduce associated harms, including medication-assisted treatment (MAT) such as opioid substitution therapy (OST), MAT plus psychosocial approaches, and residential rehabilitation. The most commonly prescribed forms of OST are the opioid agonist treatments methadone maintenance therapy (MMT) and the partial agonist buprenorphine maintenance treatment (BMT). Buprenorphine plus the antagonist naloxone (licensed as 'Subuxone') is also increasingly popular. OST is prescribed to dependent users to diminish the use and effects of illicitly acquired opioids. It is usually taken orally and therefore reduces the frequency of injection and unsafe injecting practices (Tilson 2007). As a treatment for opioid dependence, OST has been shown to increase health and social functioning, decrease crime and reduce the frequency of injection and unsafe injecting practices (Gowing 2011; Vorma 2013). Evidence suggests that OST is most effective when it is continuous and provided at adequate doses (Amato 2013; Faggiano 2003).

International evidence supports the use of combination interventions to prevent and treat HIV in PWID, with the provision of NSP, OST, and HIV antiretroviral treatment as the key interventions (Degenhardt 2010; WHO 2004). There is good evidence that NSP and OST reduce injecting risk behaviours and increasing evidence showing an impact on HIV incidence (Aspinall 2014; MacArthur 2012). However, evidence of their impact on HCV incidence among PWID, in combination or alone, is limited (Gibson 1999; Gibson 2001; Gowing 2011; Jones 2008; Palmateer 2010; Turner 2011; Van Den Berg 2007).

How the intervention might work

Two recent systematic reviews of 12 observational studies estimated that NSPs reduce HIV transmission among PWID by 48% (95% confidence interval (CI) 3% to 72%), with strong evidence that OST reduces HIV transmission by 54% (95% CI 33% to 68%) (Aspinall 2014; MacArthur 2012). However, none of the evidence was based on randomised controlled trials and either relied on cohort studies or cross-sectional studies that measured OST or NSP exposure and HIV incident infections. Previous reviews synthesising evidence of the efficacy of NSPs have focused on HIV as the main outcome (Gibson 2001; Tilson 2007; Wodak 2004), thus failing to include all the available evidence on HCV (Palmateer 2010).

A recent analysis of pooled data (N = 919) in a single country examined the effect of NSP coverage on HCV incidence, defining coverage in terms of the proportion of injections covered by a sterile syringe. This analysis suggested that high coverage of NSP ('100% NSP', i.e. obtaining at least one sterile syringes per injection) or OST (defined as receiving OST or not, either currently or within the previous 6 months) can each reduce the risk of HCV acquisition by 50%; and in combination by 80% (Turner 2011). However, due to a small number of incident HCV cases (n = 40), the efficacy estimate for 100% or more NSP among those not on OST was weak (95% CI 0.22 to 1.12), and there was insufficient power to investigate the existence of a dose-response relationship. Another systematic review examined evidence from observational studies on the impact of a range of risk reduction interventions on HCV acquisition, including behavioural interventions, NSP, and OST (Hagan 2011). This study measured the effect of NSP use, defined inconsistently due to limited available evidence, as any attendance at NSP or attendance at one point in time and showed increased risk of seroconversion among NSP attenders. Limitations of the studies included in this review were: substantial heterogeneity and lack of clarity and consistency in the measurement of NSP use across studies.

A recent review on the effect of OST use on HIV transmission identified many more studies than earlier Cochrane Reviews (MacArthur 2012). Similarly, we suspected that not all evidence on the effect of NSP on HCV transmission had been identified, so extending previous reviews would strengthen the evidence base as well as provide a more refined measure of NSP coverage that accounts for frequency of attendance and degree to which NSPs meet individuals' requirements for sterile needle/syringes.

Why it is important to do this review

Evidence of the effect of NSP with and without OST on HCV incidence is inconclusive (Palmateer 2010). Previous reviews have failed to define the frequency of use of the intervention and/or the coverage of the intervention (defined as the quantity of needles/syringes received per injection) (Hagan 2011), and a previous pooled analysis had an insufficient sample size to accurately measure the effect (Turner 2011). This review is needed in order to

estimate the effect of NSPs using a consistent definition of coverage and examining impact with and without OST on HCV incidence, in order to inform harm reduction policies aimed at reducing the burden of HCV.

OBJECTIVES

To assess the effects of needle syringe programmes and opioid substitution therapy, alone or in combination, for preventing acquisition of HCV in people who inject drugs.

We were specifically concerned with the following research questions.

1. How effective is OST alone for reducing HCV incidence in PWID?
2. How effective are needle syringe programmes (NSP) with and without OST for reducing HCV incidence in PWID?
3. How does the effect of NSP and OST vary according to duration of treatment (i.e. for NSPs weekly attendance versus monthly)?
4. How does the effect of NSP vary according to the type of service (fixed site versus mobile; high coverage versus low coverage)?
5. How does the effect of OST vary according to the dosage of OST, type of substitution used and adherence to treatment?

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), prospective and retrospective cohort studies and case-control studies. We also followed up and included prospective studies examining HCV incidence in PWID that may have collected data regarding NSPs and OST without reporting the data in the published study, or which may have reported data as part of an adjusted analysis. For these studies, we sought unpublished data relating to the impact of NSP/OST on HCV transmission via contact with study authors. We included studies only when authors provided these data.

We included cross-sectional surveys if they included a serological measure of recent infection (e.g. through positive ribonucleic acid (RNA) results on anti-body negative samples). We excluded cross-sectional studies (including serial cross-sectional studies) reporting HCV prevalence alone. We excluded studies relying on self-reported data for the outcome.

Types of participants

People who inject drugs (opioids and or stimulants). We excluded studies enrolling participants undergoing opportunistic HCV testing (outside of the study setting) and those relating to people who inject drugs in the prison setting, since addiction services and treatment provision in this setting differ significantly from community and healthcare settings.

Types of interventions

Experimental interventions

- OST
- NSP
- NSP plus OST

Studies could be based in a drug treatment facility or in the wider community, at a fixed site or mobile unit.

Exposure to OST was defined as continuous or interrupted treatment, current, recent (previous six months or duration of HCV observation period) or any past treatment with methadone or buprenorphine.

Exposure to NSP was defined as the proportion of injections covered by a clean needle/syringe or attendance at an NSP. Where it was not possible to estimate the proportion of injection covered by a clean needle/syringe, we defined exposure accounting for frequency of injection and the degree to which the NSP meets the individual's requirement for needles/syringes.

Control intervention

- No OST
- Low coverage NSP or no NSP

Types of comparisons

1. OST versus no OST
2. High NSP coverage with no OST versus low coverage NSP
3. Low NSP coverage with no OST versus no NSP
4. Combined high/low NSP coverage with OST versus no OST and low/no coverage NSP

Types of outcome measures

Primary outcomes

Our review focused on one primary outcome, HCV incidence, and no other secondary outcomes. We excluded studies that did not report on HCV incidence since they would have addressed questions outside the main review question. Incidence of HCV infection in PWID was measured via repeat testing such as detection of HCV RNA positive among HCV antibody negative results or antibody avidity. We also included studies if they reported a minimum of two HCV seroconversions (HCV antibody negative to HCV antibody positive) in participants from tests conducted at different time points.

Search methods for identification of studies

Methods to be used in this systematic review in relation to the search strategies and approaches to data synthesis follow methods applied in a similar review to assess the impact of OST on HIV incidence (MacArthur 2012).

We identified papers in four ways. Firstly, we conducted two primary searches of the literature based on key search terms identified in reviews of the effect of OST and NSP on the risk of HIV and HCV among PWID (MacArthur 2012; Palmateer 2010). The purpose of the two searches were to identify studies that measured the impact of NSP/OST on HCV incidence (see Appendix 1) and to identify longitudinal studies that measured HCV incidence and reported the impact of NSP/OST as part of an adjusted analysis (see Appendix 2). The Cochrane Drugs and Alcohol Group Trials Search Co-ordinator reviewed the search strategy and conducted the search.

Electronic searches

We searched for relevant studies in the following sources.

- The Cochrane Drugs and Alcohol Group Specialised Register of Trials (searched 16 November 2015).
- The Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 11).
- The Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library, 2015, issue 11).
- The Database of Abstracts of Reviews of Effects (DARE)(Cochrane Library, 2015, issue 11).
- The Health Technology Assessment Database (HTA) (Cochrane Library, 2015, issue 11).
- The NHS Economic Evaluation Database (NHSEED) (Cochrane Library, 2015, issue 11).
- MEDLINE (Ovid) (1966 to 16 November 2015).
- Embase (embase.com) (1974 to 16 November 2015).
- The Database of Abstracts of Reviews of Effects (DARE) (Cochrane Library, searched 16 November 2015).
- Global Health (Ovid) (1974 to 16 November 2015).
- CINAHL (EBSCOhost) (1982 to 16 November 2015).
- Web of Science (1991 to 16 November 2015).
- PsycINFO (Ovid) (1985 to 16 November 2015).

We searched for ongoing clinical trials and unpublished trials via searches of the following websites.

- ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).

This review fully incorporates the results of searches conducted up to November 2015. We identified a further four reports of studies in a search update conducted in March 2017. We have added those studies to Studies awaiting classification and will incorporate them into the review at the next update.

Searching other resources

We searched the publications of key international agencies including the European Monitoring Centre on Drugs and Drug Addiction, the European Centre for Disease Control, the National Institute on Drug Abuse, the US Institute of Medicine, the United Nations Office on Drugs and Crime Prevention and the World Health Organization. We handsearched the reference lists of relevant articles to identify additional relevant studies and contacted experts in the field to identify ongoing research. We also searched conference abstracts including the International Harm Reduction Conference, International HIV/AIDS Society and the European Association for the Study of the Liver conference. Finally we contacted principal investigators and authors of prospective studies that had examined HCV incidence in PWID but had not reported on the intervention exposure to see whether these data were available from unpublished sources.

There were no language or date restrictions, and we included peer reviewed and non-peer reviewed papers.

Data collection and analysis

Selection of studies

Two reviewers (LP, SM) independently screened all titles and abstracts, resolving disagreements following discussion. Two reviewers (LP, SM) independently screened full-text copies of relevant articles to determine whether they met eligibility criteria for direct inclusion or for contact of study authors. We resolved disagreements by discussion or, where disagreements persisted, with adjudication by a third author (JR) to enable a consensus.

We had full-text papers in languages other than English translated by individuals fluent in those languages. Where there were multiple publications from the same study, or the same city or region, we selected all published papers and extracted data from the study with the greatest number of outcome events (i.e. HCV seroconversions).

Data extraction and management

One author (LP) extracted data using a data extraction form, which two review authors had pre-piloted to determine suitability for capturing study data and assessing quality. A second author (JR) checked all data to assess the accuracy of data extraction. Data extracted included:

- lead author;
- review title or unique identifier and date;
- eligibility for inclusion;
- reasons for exclusion;
- study aim(s);
- study design (included sampling methods, participant and attrition rate);
- study location;
- study setting;
- proportion of participants who injected opioids;
- proportion of participants who injected stimulants;
- definition of exposure (recency of injecting);
- intervention (NSP provision; number of needles distributed; frequency of injection; frequency of attendance; methadone maintenance therapy or buprenorphine maintenance treatment; delivery (e.g. continuous versus interrupted treatment); duration; dose);
- additional interventions or incentives provided alongside NSP/OST;
- participants (number in each intervention group; age, sex and ethnicity);
- duration of follow-up in each treatment arm;
- outcome measure (HCV seroconversion) overall and by NSP and OST exposure;
- unadjusted and adjusted effect size: incidence rate ratio (IRR); odds ratio (OR); risk ratio (RR)hazard ratio (HR) and precision (i.e. 95% confidence interval (CI));
- confounding factors used to adjust effect estimates including high-risk behaviours (injecting risk behaviours, frequency of injection, homelessness, experience of prison, duration of injection, or age, poly drug use);
- background prevalence of HCV in the population;
- any other comments.

Assessment of risk of bias in included studies

We would have performed the 'Risk of bias' assessment for RCTs using the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The recommended approach is a two-part tool, addressing seven specific domains, namely

sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry, in terms of low, high or unclear risk. To make these judgments we would have used the criteria indicated by Higgins 2011 , adapted to the addiction field. See Appendix 3 for details. We would have assessed the risk of bias for unpublished estimates by referring to the study methods in the corresponding published paper.

We assessed the risk of bias in non-randomised studies using a pilot version of a tool in development by the Methods Groups of the Cochrane Collaboration (Sterne 2013). This was undertaken as part of the formal piloting of the tool, in collaboration with its developers. The seven-domain tool is an extension of the existing tool for assessing risk of bias in randomised trials (Higgins 2011).

Three domains concern the pre-intervention phase or intervention phase.

1. Baseline confounding. In assessing bias due to confounding we considered there to be two critically important confounders: duration of injecting or age; and frequency of injecting.
2. Selection of participants into the study.
3. Measurement of the intervention.

Four domains relate to the post intervention phase.

1. Departures from intended interventions (performance bias).
2. Missing data (attrition bias).
3. Measurement of outcomes or interventions (detection bias).
4. Selection of the reported results (outcome reporting bias).

Finally, we gave an overall risk of bias judgment at the study level for each relevant outcome (see Appendix 4).

Since we were piloting a new 'Risk of bias' tool, four contributors initially applied it independently to a sample of four studies. We discussed and compared assessments to ensure consistent interpretation of domains. Two people independently assessed the remaining studies in the review and compared results. We resolved disagreements by discussion.

Measures of treatment effect

When trials reported only effect estimates, we directly extracted unadjusted and adjusted estimates reported as ORs, risk ratios (RRs), IRRs or HRs with 95% CIs. When studies provided only incidence data, we estimated rate ratios and 95% CIs based on the person-years of observation. We extracted effect estimates reported as ORs and took them as an approximation of the RR, even though the incidence of HCV in included studies was variable (mean 18.7/100 person-years, range 0.09 to 42). In order to account for this, we explored the impact of removing ORs on our overall intervention effect in sensitivity analyses(MacArthur 2012; Zhang 1998).

Dealing with missing data

We contacted study authors if studies provided data regarding use of NSP or the impact of drug treatment on HCV transmission but insufficient detail regarding the precise form of treatment provided. We also contacted study authors if papers reported HCV incidence data but no data regarding drug treatment or NSP. If we could not obtain missing data, we excluded the studies from the review.

Assessment of heterogeneity

We assessed heterogeneity via inspection of the forest plot and by a Chi^2 test to demonstrate whether the observed differences in results were compatible with chance alone. We calculated tThe I^2 statistic was calculated to examine the percentage of variability due to heterogeneity rather than to sampling error. We explored heterogeneity through sensitivity and subgroup analysis.

Assessment of reporting biases

We used funnel plots (plots of the effect estimate from each study against the sample size or effect standard error) to assess the potential for bias related to the size of the trials, which could indicate possible publication bias. We inspected funnel plot symmetry when there were at least 10 studies included in the meta-analysis.

Data synthesis

We used a random-effects model for all analyses, allowing for heterogeneity between studies and converting all effect estimates into RRs. We pooled adjusted and unadjusted effect estimates in separate meta-analyses. We used Review Manager 5 (RevMan 5) for statistical analyses (RevMan 2014). We pooled data across different observational study designs and assessed the potential association between study design and effect size, stratifying by study design as well as in meta-regression analyses.

Subgroup analysis and investigation of heterogeneity

We examined heterogeneity with the I^2 and Tau^2 statistic and explored reasons for heterogeneity using univariable random-effects meta-regression to evaluate the impact of the following covariates: geographical region of study; recruitment setting (community-based or treatment); percentage of female participants; main drug injected; type of NSP; frequency of injecting; dose, duration and adherence to NSP/OST (i.e. continuous or interrupted treatment); and study design. There was insufficient information to assess the impact of adherence to NSP/OST (i.e. continuous or interrupted treatment).

Sensitivity analysis

We excluded studies that we assessed as being at critical risk of bias. We also used sensitivity analysis to determine to what extent the overall intervention effect changed when we excluded studies: at severe or unclear risk of bias; that did not adjust for confounders; from unpublished datasets; and that used odds ratios as effect measures and were cross-sectional in design.

Summary of findings table

We assessed the overall quality of the evidence for the primary outcome using the GRADE system for assessing the quality of evidence (GRADE 2004; Guyatt 2008; Guyatt 2011; Schünemann 2006). GRADE takes into account issues not only related to internal validity but also to external validity, such as directness of results. The 'Summary of findings' tables present the main findings of the review in a transparent and simple tabular format. In particular, they provide key information concerning the quality of evidence,

the magnitude of effect of the interventions examined and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence.

- *High*: we are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- *Very low*: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons.

- Serious (−1) or very serious (−2) study limitation for risk of bias.
- Serious (−1) or very serious (−2) inconsistency between study results.
- Some (−1) or major (−2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review).
- Serious (−1) or very serious (−2) imprecision of the pooled estimate(−1).
- Publication bias strongly suspected (−1).

Grading is increased for observational studies for the following reasons.

- Strong evidence of association - significant relative risk of more than 2.0 (or less than 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1).
- Very strong evidence of association - significant relative risk of more than 5.0 (or less than 0.2) based on direct evidence with no major threats to validity (+2).
- Evidence of a dose response gradient (+1).
- All plausible confounders would have reduced the effect (+1).

RESULTS

Description of studies

Results of the search

We identified 6720 unique records from database searching and from reference lists of included studies and relevant reviews. We excluded 6576 on the basis of title and abstract and retrieved 144 full-text articles for more detailed evaluation. We excluded 103 of these (referring to 101 studies) after reading the full text because they did not meet the inclusion criteria; we characterised 6 studies as awaiting classification since they were written in Chinese or German, and we were not able to translate.

We finally included 28 studies (31 references): 21 published and 7 unpublished reports that satisfied all criteria required for inclusion in the review. See Figure 1.

Figure 1. Study flow diagram.

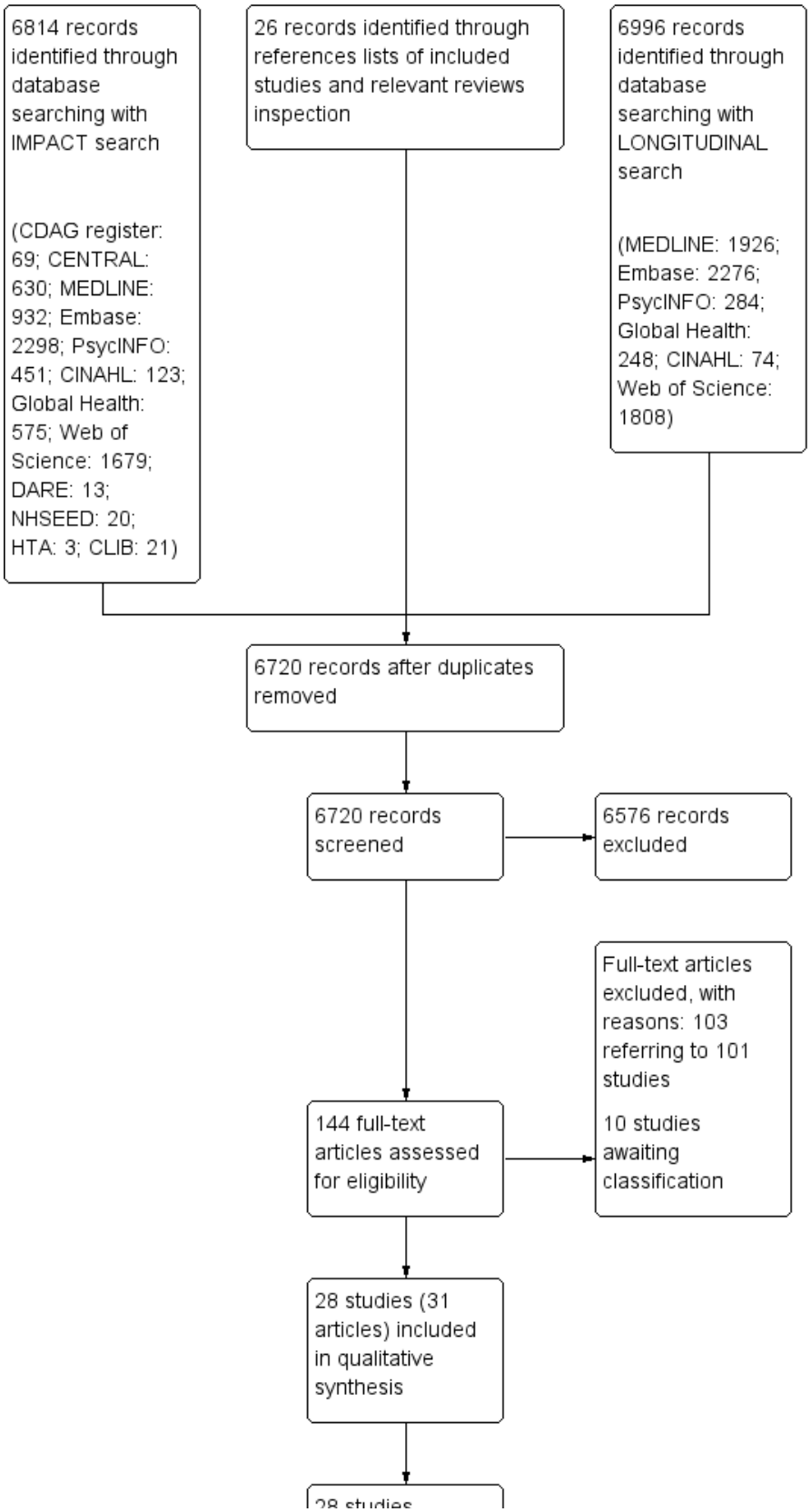
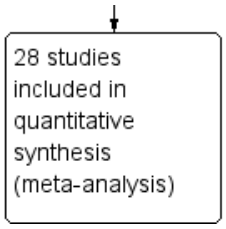


Figure 1. (Continued)



Twenty-one papers directly included measures of the impact of exposure to either OST or NSP on HCV acquisition. In addition, we identified 11 eligible prospective studies that measured HCV incidence and contacted authors of these articles. Of these, we obtained unpublished data from six cohort studies in Montreal, Canada (Bruneau 2015 [pers comm]); Baltimore, USA (Mehta 2015 [pers comm]), San Francisco, USA (Page 2015 [pers comm]); London, UK (Judd 2015 [pers comm]); Melbourne, Australia (Aitken 2015 [pers comm]); and Sydney, Australia (Maher 2015); plus one cross-sectional survey (Hope 2015 [pers comm]).

Included studies

See Characteristics of included studies.

In total we included 21 published studies (Craine 2009; Crofts 1997; Hagan 1995; Hagan 1999; Holtzman 2009; Hope 2011; Lucidarme 2004; Nolan 2014, Palmateer 2014a ; Patrick 2001; Rezza 1996; Roy 2007; Ruan 2007; Spittal 2012; Thiede 2000; Thorpe 2002; Tsui 2014; Vallejo 2015; Van Beek 1998; Van Den Berg 2007; White 2014), plus 7 unpublished studies (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Hope 2015 [pers comm], Judd 2015 [pers comm]; Maher 2015 Mehta 2015 [pers comm]; Page 2015 [pers comm]), comprising 1817 HCV incident infections and 8806.95 person-years of follow-up. HCV incidence in the 28 studies ranged from 0.09 and 42 cases per 100 person-years.

Design

We did not identify any randomised controlled trials. We included 2 case-control studies (Hagan 1995, Rezza 1996), 3 cross-sectional studies (Hope 2011; Hope 2015 [pers comm]; Palmateer 2014a), 20 prospective cohort studies (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Craine 2009; Hagan 1999; Holtzman 2009; Judd 2015 [pers comm]; Lucidarme 2004; Maher 2015; Mehta 2015 [pers comm]; Nolan 2014; Page 2015 [pers comm]; Patrick 2001; Ruan 2007; Spittal 2012; Thiede 2000; Thorpe 2002; Tsui 2014; Vallejo 2015; Van Den Berg 2007; White 2014); 2 retrospective cohort studies (Crofts 1997; Van Beek 1998); and 1 serial cross-sectional survey (Roy 2007).

Duration of trials

For cohort studies the duration of follow-up ranged between 1 and 22 years. Included studies were published between 1995 and 2014.

Participants and setting

Twenty-five studies reported participants' sex, and the mean proportion of female participants was 32% (range 2.8% to 55.9%). Across 14 studies, on average 40.7% (range 9.2% to 69.2%) of participants had experience of recent or past homelessness, and 35% (range 18.2% to 90%) had experience of prison (12 studies). The mean reported use of stimulants was 32.7% (range 0% to 75%, 19 studies) and a mean of 50.5% (range 18.2% to 100%) reported heroin use (13 studies). Across 14 studies a mean of 50.6% of participants reported injecting daily (range 18.2% to 84%).

Most study participants were currently injecting at the time of recruitment, with eligibility criteria for study participation stated as: injection in the previous four weeks (Craine 2009; Hope 2011; Hope 2015 [pers comm]; Judd 2015 [pers comm]; Nolan 2014; Page 2015 [pers comm]; Patrick 2001; Spittal 2012; Thiede 2000; Tsui 2014; Vallejo 2015), in the previous 3 months to 6 months (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Hagan 1995; Maher 2015; Roy 2007; Ruan 2007; Thorpe 2002), or in the previous 6 months to 12 months (Hagan 1999; Holtzman 2009; Palmateer 2014a; White 2014). A few studies included PWID who had injected at any time in the past (Lucidarme 2004, Mehta 2015 [pers comm]; Van Den Berg 2007), or they reported no information on recency of injection (Crofts 1997; Rezza 1996; Van Beek 1998).

Eight studies took place in the USA; five each in the UK, Canada and Australia; and one each in the Netherlands, France, Italy, Spain and China.

Study size and method of recruitment

Sample size ranged from 46 and 2788. The method of recruitment primarily involved street outreach, in 13 studies (Craine 2009; Crofts 1997; Hagan 1995; Hagan 1999; Lucidarme 2004; Page 2015 [pers comm]; Palmateer 2014a; Rezza 1996; Roy 2007; Thiede 2000; Tsui 2014; Van Beek 1998; Van Den Berg 2007); respondent-driven sampling, in 3 studies (Holtzman 2009; Hope 2011; Hope 2015 [pers comm]); and service attenders (both low-threshold community services and drug treatment), in 12 studies (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Judd 2015 [pers comm]; Maher 2015; Mehta 2015 [pers comm]; Nolan 2014; Patrick 2001; Ruan 2007; Spittal 2012; Thorpe 2002; Vallejo 2015; White 2014). Most studies drew on a combination of recruitment methods.

Types of interventions

Twenty-one of the included studies assessed the impact of OST (Craine 2009; Crofts 1997; Lucidarme 2004; Nolan 2014; Palmateer 2014a; Rezza 1996; Ruan 2007; Spittal 2012; Thiede 2000; Tsui 2014; Vallejo 2015; Van Beek 1998; Van Den Berg 2007; White 2014), including seven unpublished estimates (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Hope 2015 [pers comm]; Judd 2015 [pers comm]; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]).

Current use of OST was defined as: reporting use of prescribed methadone or buprenorphine within the previous six months (yes or no) (Bruneau 2015 [pers comm]; Maher 2015; Nolan 2014; Rezza 1996; White 2014); use for more than six months (Judd 2015 [pers comm]), use of methadone or buprenorphine at the time of survey

(Craine 2009; Hope 2015 [pers comm]; Mehta 2015 [pers comm]; Palmateer 2014a; Spittal 2012), or continuous use of methadone throughout follow-up period (Crofts 1997; Lucidarme 2004; Thiede 2000). Van Den Berg 2007 defined continuous use as daily use of methadone (any dosage) in the previous six months, while Aitken 2015 [pers comm] defined it as in the previous one month. Tsui 2014 used a three-month time frame to measure use of OST (methadone or buprenorphine).

Seventeen studies assessed the impact of NSP (Hagan 1995; Hagan 1999; Holtzman 2009; Hope 2011; Palmateer 2014a; Patrick 2001; Roy 2007; Thorpe 2002; Vallejo 2015; Van Den Berg 2007; White 2014), including five unpublished sources (Bruneau 2015 [pers comm]; Hope 2015 [pers comm]; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]).

Bruneau 2015 [pers comm] defined high NSP coverage as obtaining 100% of needles/syringes from a safe source (receiving one clean needle for every injection), Hope 2011, Hope 2015 [pers comm]and Van Den Berg 2007 defined it as reporting ≥100% of injections using clean needles/syringes (receiving one or more clean needle for every injection), and Palmateer 2014a defined it as reporting ≥200% of injections with clean syringes (receiving more than two clean needles for every injection). Other measures of high coverage were defined as regular attendance at least once per week at an NSP in Patrick 2001 or obtaining most needles/syringes from an NSP in the last six months (Hagan 1999).

Low-level NSP coverage was defined as ever having used an NSP (Hagan 1995), using NSPs in the previous one to six months (Holtzman 2009; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]; Roy 2007; Thorpe 2002; White 2014), or having less than 100% of injections covered by a clean needle/syringe in the last six months (Hope 2011; Van Den Berg 2007).

Four studies assessed the impact of combined NSP with OST (Hope 2011; Palmateer 2014a; Van Den Berg 2007), including one unpublished data source (Bruneau 2015 [pers comm]). Studies defined combined use of NSP plus OST in two ways: high NSP coverage plus current use of OST (Bruneau 2015 [pers comm]; Hope 2011; Palmateer 2014a; Van Den Berg 2007), and OST use plus low NSP coverage (Hope 2011; Palmateer 2014a; Van Den Berg 2007). One study looked at the impact of uptake of injecting paraphernalia (defined as spoons and filters) alone, with needles/syringes and in combination with OST (Palmateer 2014a).

Excluded studies

See Characteristics of excluded studies.

We excluded 101 studies (104 articles). Grounds for exclusion were: no outcome of interest assessed (43 studies); no intervention of interest (32 studies); no comparison of interest (all participants on OST, 9 studies); no outcome and no intervention of interest (11 studies); no outcome and no comparison of interest (4 studies); and editorial or overview (2 studies).

Risk of bias in included studies

Bias due to baseline confounding

We judged 12 studies to be at moderate risk of bias due to confounding because they adjusted for critical confounders (duration of injecting or age, and frequency of injecting) and used a suitable analysis method (e.g. adjusted for time-varying confounding if appropriate) (Bruneau 2015 [pers comm]; Hagan 1999; Hope 2011; Hope 2015 [pers comm]; Judd 2015 [pers comm]; Lucidarme 2004; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]; Thiede 2000; Tsui 2014; White 2014). We judged 12 to be at serious risk because confounding was insufficiently addressed in the analyses (Craine 2009; Hagan 1995; Holtzman 2009; Nolan 2014; Palmateer 2014a; Patrick 2001; Rezza 1996; Roy 2007; Spittal 2012; Thorpe 2002; Vallejo 2015; Van Den Berg 2007). The four studies we assessed as being at critical risk did not make any adjustment for confounding (Aitken 2015 [pers comm]; Crofts 1997; Ruan 2007; Van Beek 1998).

Bias in the selection of participants into the study

We deemed five studies to be at moderate risk of bias because start of follow-up and start of intervention coincided for all or most subjects (Hope 2011; Hope 2015 [pers comm]; Patrick 2001; Thiede 2000; Tsui 2014). We judged three studies to be at critical risk of bias because selection into the study was strongly related to intervention and outcome (Aitken 2015 [pers comm]; Judd 2015 [pers comm]; Ruan 2007). We considered the remaining studies to be at serious risk of selection bias, largely because participants may have already been exposed to the intervention prior to the start of the study. For two studies (Mehta 2015 [pers comm]; Page 2015 [pers comm]), we did not have enough information to make a judgment.

Bias in measurement of the intervention

We judged five studies to be at low risk of bias because intervention status was well defined and based solely on information collected at the time of intervention (Crofts 1997; Hagan 1999; Thiede 2000; Tsui 2014; Vallejo 2015). We deemed seven studies to be at moderate risk because some aspects of the assignments of intervention status were determined retrospectively (Bruneau 2015 [pers comm]; Holtzman 2009; Nolan 2014; Palmateer 2014a; Spittal 2012; Van Den Berg 2007; White 2014). We considered Judd 2015 [pers comm] to be at critical risk of bias because there was considerable risk of misclassification of intervention status. We judged the remaining studies to be at serious risk of selection bias mainly because intervention status was not well defined. For two studies (Mehta 2015 [pers comm]; Page 2015 [pers comm]), we did not have enough information to make a judgment.

Blinding

Departures from intended interventions: none of the studies provided information about co-interventions received by participants or changes in treatment, so we coded departures from intended interventions as 'no information' for all studies.

Measurement of outcomes: we deemed all but one study to be at low risk of bias in relation to measurement of the outcome since HCV seroconversion was laboratory-confirmed, and testing was carried out at pre-defined time points, with no apparent differences between intervention groups. InCrofts 1997, the risk was serious because there may have been differential testing (for participants not on methadone, the need for HCV testing was determined according to the clinician's judgment).

Incomplete outcome data

Six studies were at a low risk of bias because data were reasonably complete (Hagan 1995; Hagan 1999; Hope 2011; Nolan 2014; Spittal 2012; Thiede 2000), and two studies were at moderate

risk of bias because there were no substantial differences in the proportions of missing data or in reasons for missing data across intervention groups (Thorpe 2002; Tsui 2014). The eight studies at serious risk (Craine 2009; Crofts 1997; Lucidarme 2004; Palmateer 2014a; Patrick 2001; Ruan 2007; Vallejo 2015; Van Den Berg 2007), and the five at critical risk (Aitken 2015 [pers comm]; Judd 2015 [pers comm]; Rezza 1996; Roy 2007; Van Beek 1998), had substantial differences in either the proportions of missing participants or the reasons for missing data across interventions, and investigators did not adjust for these differences in the analyses. Seven studies provided insufficient information about missing data or the potential for data to be missing (Bruneau 2015 [pers comm]; Holtzman 2009; Hope 2015 [pers comm]; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]; White 2014).

Selective reporting

We judged all studies to be at low risk for selective reporting as the measure of the outcome of interest was clearly defined and internally consistent. For one study (Aitken 2015 [pers comm]), there was insufficient information for assessing reporting bias.

Overall risk of bias

We judged only 2 studies to be at moderate overall risk of bias (Thiede 2000; Tsui 2014), while 17 were at serious overall risk (Bruneau 2015 [pers comm]; Craine 2009; Hagan 1995; Hagan 1999; Holtzman 2009; Hope 2011; Lucidarme 2004; Maher 2015; Nolan 2014; Palmateer 2014a; Patrick 2001; Spittal 2012; Thorpe 2002; Vallejo 2015; White 2014), and 7 were at critical risk (Aitken 2015 [pers comm]; Crofts 1997; Judd 2015 [pers comm]; Rezza 1996; Roy 2007; Ruan 2007; Van Beek 1998). For two studies, we did not have enough information to make a judgment (Mehta 2015 [pers comm]; Page 2015 [pers comm]). This is summarised in Table 1.

Effects of interventions

See: **Summary of findings for the main comparison** Current OST versus no OST for people who inject drugs; **Summary of findings 2** High NSP coverage versus no/low NSP coverage for people who inject drugs; **Summary of findings 3** Combined OST and high NSP versus no OST and low/no NSP for people who inject drugs

1. Current use of OST versus no current OST

Of the 20 studies that assessed the impact of OST on HCV incidence, we pooled data from 17 studies that measured current OST (Craine 2009; Crofts 1997; Lucidarme 2004; Nolan 2014; Palmateer 2014a; Rezza 1996; Spittal 2012; Thiede 2000; Tsui 2014; Vallejo 2015; Van Den Berg 2007; White 2014), including five unpublished estimates (Aitken 2015 [pers comm]; Bruneau 2015 [pers comm]; Hope 2015 [pers comm]; Judd 2015 [pers comm]; Maher 2015).

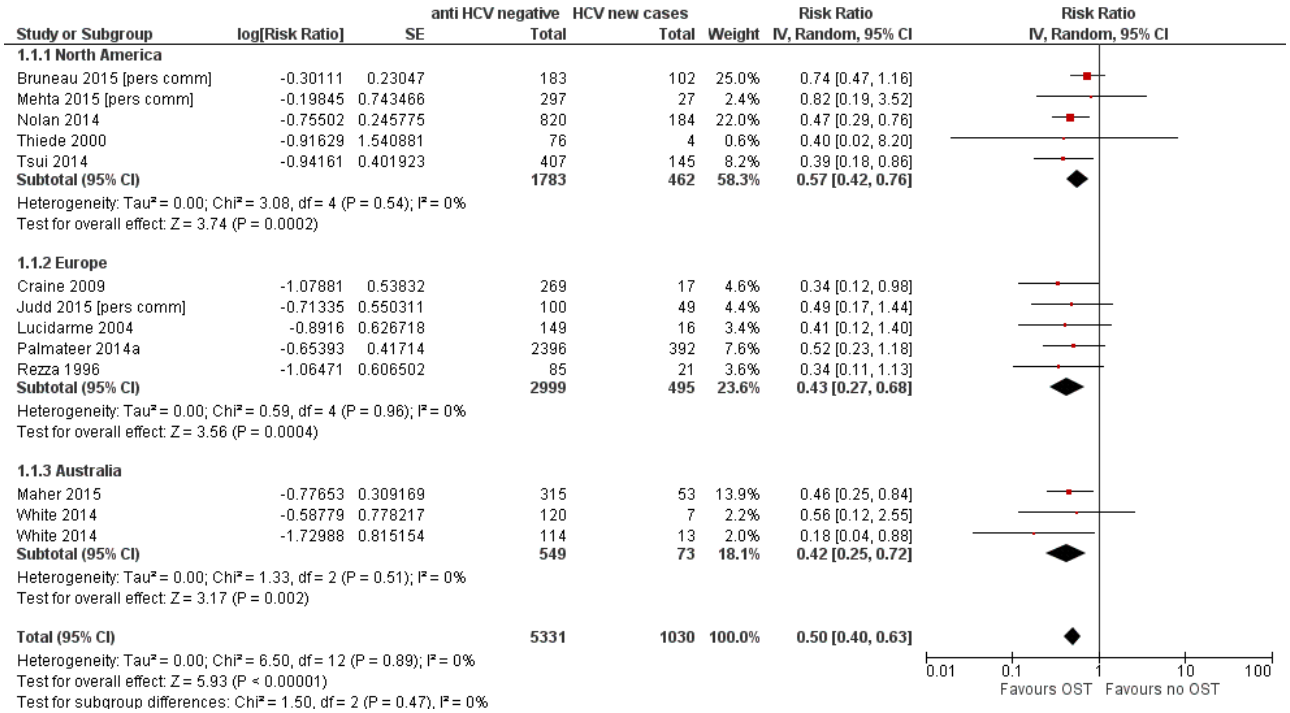
Fourteen of the included studies were longitudinal studies, one used a case-control study design (Rezza 1996), and two were cross-sectional surveys (Hope 2015 [pers comm]; Palmateer 2014a). A total of 1148 HCV incident cases were included over 6553.1 person-years of follow-up.

The primary analyses were focused on twelve studies presenting adjusted estimates. These analyses included the following effect measures: hazard ratios in six studies (Bruneau 2015 [pers comm]; Lucidarme 2004; Maher 2015; Tsui 2014; White 2014), odds ratios in five studies (Judd 2015 [pers comm]; Nolan 2014; Palmateer 2014a; Rezza 1996; Thiede 2000), and incident rate ratio in two studies (Craine 2009; Mehta 2015 [pers comm]).

Adjusted estimates controlled for potential confounding effects of the following factors: duration and frequency of injection (Bruneau 2015 [pers comm]; Judd 2015 [pers comm]); area of residence, homelessness, sharing injecting equipment or needles (Craine 2009); sex, geographical region, use of condoms, injection of cocaine, duration of injection, sharing injecting equipment (Lucidarme 2004); duration of injection, frequency of injection and age of whole cohort (Mehta 2015 [pers comm]); unstable housing, cocaine, heroin or methamphetamine injection, cohort of recruitment, year of recruitment, follow-up time (Nolan 2014); survey year, homelessness, stimulant injection, duration of injection (Palmateer 2014a); sex, age, duration of drug use, injection of cocaine (Rezza 1996); age, duration of injection, sex, ethnicity, homelessness or prison in the last 3 months (Tsui 2014); sex, ethnicity, age, frequency of injecting and sharing needles/syringes (White 2014); and injected at follow-up, pooled money to buy drugs, injected with used needles and backloading (removing the plunger from a syringe and filling it with drug solution from another needle/syringe) (Thiede 2000).

Random-effects meta-analysis of multivariable estimates showed that opioid substitution therapy was associated with a 50% reduction in the risk of HCV infection (RR 0.50 95% CI 0.40 to 0.63) with little heterogeneity between 12 studies involving 6361 participants (I^2 = 0%, P = 0.89, Tau^2 = 0.00; Analysis 1.1; Figure 2).

Figure 2. Forest plot of comparison: 1 Current OST versus no OST, outcome: 1.1 HCV incidence adjusted analyses by region.



Sensitivity analysis

The intervention effect strengthened when we excluded estimates from four unpublished data sources (Bruneau 2015 [pers comm]; Judd 2015 [pers comm]; Maher 2015; Mehta 2015 [pers comm]): RR 0.42 (95% CI 0.31 to0.58; Analysis 2.1; I^2 = 0%, Tau^2 = 0.00, 8 studies, N = 5235).

This effect was maintained when the analysis was limited to excluding Judd 2015 [pers comm] and Rezza 1996, judged to be at critical risk of bias, and Mehta 2015 [pers comm], which reported insufficient information to give an overall risk of bias assessment (RR 0.51, 95% CI 0.40 to 0.64; Analysis 3.1 I^2 = 0%, Tau^2 = 0.00). The intervention effect was also unchanged when the analysis excluded Palmateer 2014a and Rezza 1996, two cross-sectional studies that reported baseline measures of effect only (RR 0.51, 95% CI 0.40 to 0.65; Analysis 4.1; I^2 = 0.0%, Tau^2 = 0.00, 10 studies, N = 3367).

Random-effects meta-analysis of 16 studies that presented unadjusted estimates shows that current OST was associated with a 43% reduction in the risk of HCV acquisition (RR 0.57, 95% CI 0.45 to 0.73; Analysis 5.1; 16 studies, N = 10,647), with only moderate evidence of heterogeneity between studies (I^2 = 32.4%, P = 0.09, Tau^2 = 0.08).

Meta-regression

Based on univariable meta-regression of unadjusted estimates, we found no evidence that effectiveness varied by other covariates including geographical location (Analysis 1.1) or study design (Analysis 1.2). We did find evidence of differential impact in the proportion of female participants in the sample. With each 10% increase of female participants in sample, the effect of intervention exposure was reduced (ratio of rate ratios = 1.59, 95% CI 1.13 to 2.29; Table 2).

History of OST

Three studies published unadjusted estimates of lifetime use of OST versus never using OST, comprising 115 HCV cases over 511.6 person-years from three prospective cohorts (Ruan 2007; Vallejo 2015; Van Beek 1998). One study did not define the time frame, so we coded it as lifetime experience of OST (Vallejo 2015).

Three studies published unadjusted estimates of interrupted OST use versus no interruption of use (Crofts 1997; Nolan 2014; Thiede 2000). Two of these studies were prospective cohorts and one retrospective; they included a total of 200 HCV cases over 2273.8 person-years. Interrupted OST use was defined either as use of MMT at baseline but not at follow-up (Nolan 2014), or leaving MMT at least once during follow-up (Crofts 1997; Thiede 2000).

One prospective cohort study comprising 149 HCV cases over 680 person-years examined OST for detoxification (Tsui 2014), and two studies measured high (60 mg or more) or low dosage (less than 60 mg) methadone in the last 6 months (Bruneau 2015 [pers comm]; Van Den Berg 2007). Both these studies were prospective cohorts and included 148 HCV cases over 598.6 person-years.

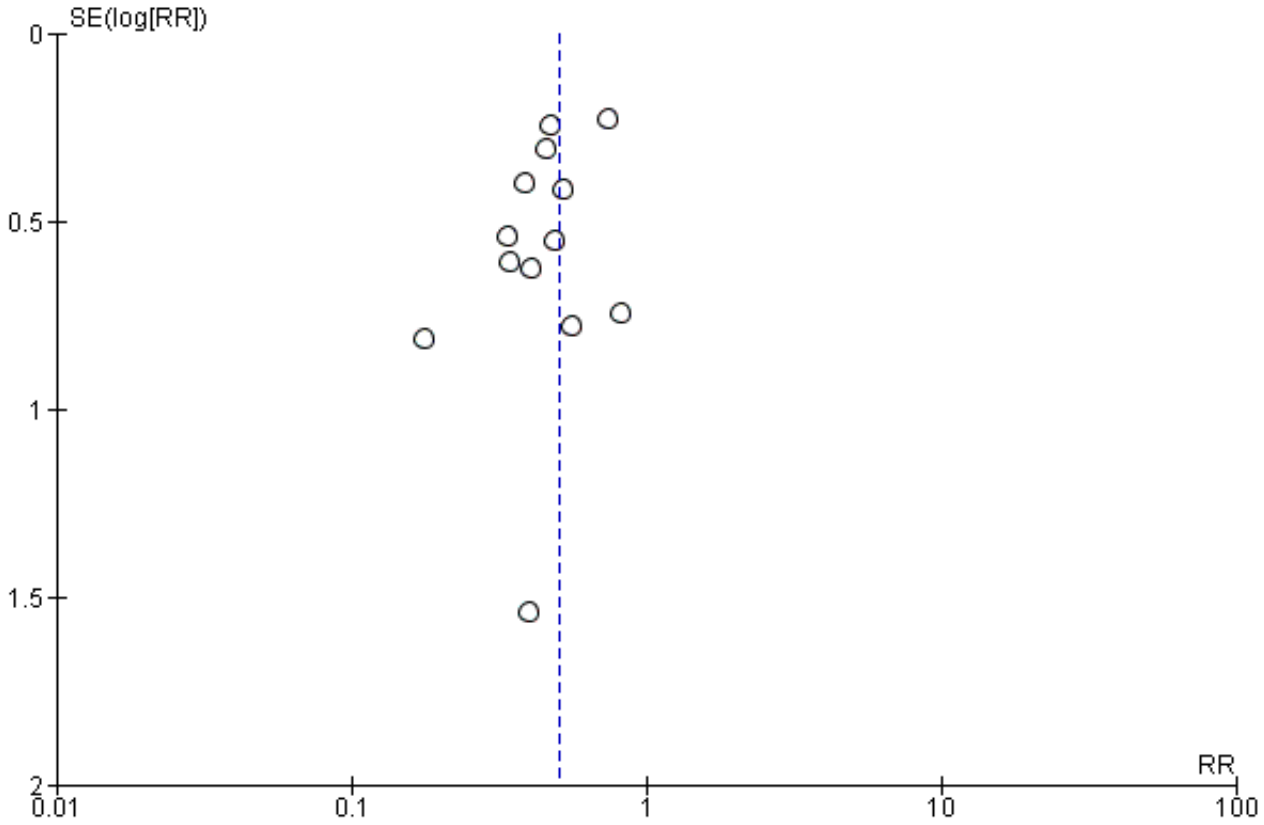
Random-effects meta-analysis showed a very weak protective effect for lifetime (RR 0.81, 95% CI 0.52 to 1.27, I^2 = 0%, Tau^2 = 0.00, 3 studies, N = 385) or interrupted use of OST (RR 0.80, 95% CI 0.57 to 1.10, I^2 = 86.1%, Tau^2 = 0.05, 3 studies, N = 1157). The one study measuring the impact of OST used for detoxification was not associated with reduced HCV risk acquisition (RR 1.45, 95% CI 0.79 to 2.66, Tau^2 = 0.00, N = 552). In the two studies that categorised OST dosage and HCV acquisition, we found a moderate association for

those exposed to high dosage OST (RR 0.52, 95% CI 0.29 to 0.94, I^2 = 27.2%, Tau^2 = 0.05, N = 453) and a very weak association for those exposed to low dosage OST (RR 0.85, 95% CI 0.44 to 1.65; Analysis 1.3; I^2 = 61.2%, Tau^2 = 0.14, N = 453).

Publication bias

A funnel plot of 13 estimates (12 studies) suggested no evidence of publication bias in studies of current OST exposure (Figure 3).

Figure 3. Funnel plot of comparison: 1 Current OST versus no OST, outcome: 1.1 HCV incidence adjusted analyses by region.



2. Needle syringe programmes versus lower or no NSP coverage

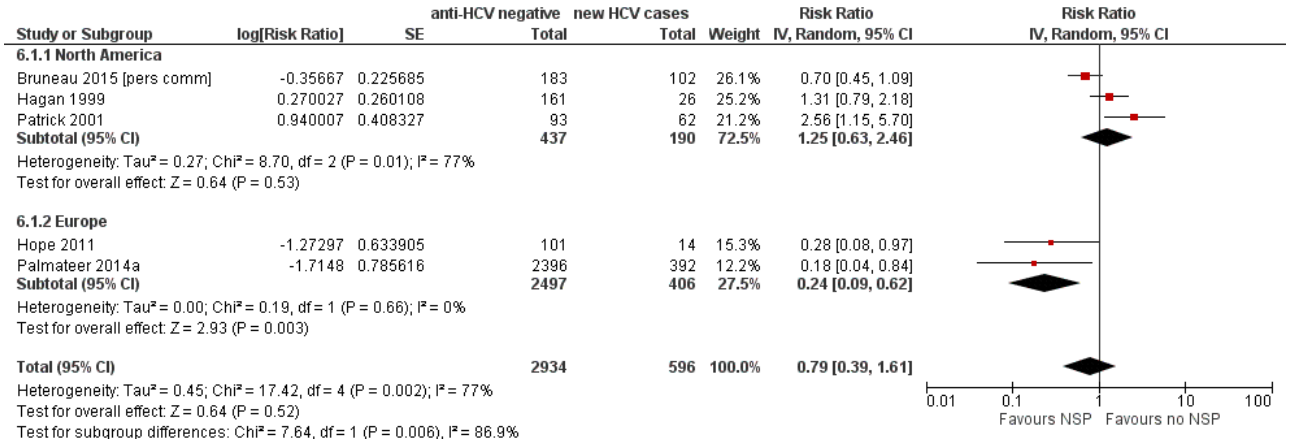
Of the 15 studies that reported measures of NSP exposure and HCV incidence, comparison groups consisted of NSP non-attendance (Hagan 1995; Hagan 1999; Holtzman 2009; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]; Patrick 2001; Roy 2007; Thorpe 2002; Van Den Berg 2007), lower coverage of injections covered by a clean needle/syringe (Hope 2011; Hope 2015 [pers comm]; Palmateer 2014a; Van Den Berg 2007), and non-attendance at NSP and not using a safe source for obtaining needles/syringes (Bruneau 2015 [pers comm]).

2.1 High coverage versus non-attendance or lower coverage

Five studies reported adjusted measures of high NSP coverage and HCV incidence (Hagan 1999; Hope 2011; Palmateer 2014a; Patrick 2001), including one unpublished dataset (Bruneau 2015 [pers comm]). Three were prospective cohorts (Bruneau 2015 [pers comm], Hagan 1999, Patrick 2001), and two were cross-sectional surveys (Hope 2011; Palmateer 2014a), comprising 407 HCV cases over 1644 person-years. Effect measures used in these studies included: hazard ratios in two studies (Bruneau 2015 [pers comm], Patrick 2001), odds ratios in two studies (Hope 2011; Palmateer 2014a), and risk ratio in one study (Hagan 1999).

Random-effects meta-analysis showed weak evidence that high coverage NSP was not associated with reduced risk of HCV infection (RR 0.79, 95% CI 0.39 to 1.61) derived from 5 studies with 3530 participants and high heterogeneity between studies (I^2 =77%, P = 0.002, Tau^2=0.44; Figure 4; Analysis 6.1).

Figure 4. Forest plot of comparison: 2 High NSP coverage versus no/low NSP coverage, outcome: 2.1 HCV incidence adjusted analyses by region.



Sensitivity analyses

Evidence of any intervention effect became weaker after excluding the unpublished dataset of Bruneau 2015 [pers comm] (RR 0.77, 95% CI 0.28 to 2.13; Analysis 7.1; Tau^2 = 0.81, 4 studies, N = 3245). We did not rate any studies as being at critical risk of bias. The intervention effect disappeared when we excluded Hope 2011 and Palmateer 2014a, two cross-sectional studies (RR 1.25, 95% CI 0.63 to 2.46; Analysis 8.1; I^2 = 77.0%, Tau^2 = 0.27, 3 studies, N = 627).

Random-effects meta-analysis of seven studies that presented unadjusted estimates show that the weak intervention effect was unchanged (RR 0.78, 95% CI 0.39 to 1.55; Analysis 9.1; I^2 = 79%, Tau^2 = 0.72).

Meta-regression

Based on univariable meta-regression analyses, we found evidence that the effectiveness of high NSP coverage varied according to geographical region. High NSP coverage was associated with a 76% reduction in HCV acquisition risk (RR 0.24, 95% CI 0.09 to 0.62), with less heterogeneity between two European studies in 2903 participants (I^2 = 0%, P = 0.66). There was no evidence of an intervention effect from studies in North America (RR 1.25, 95% CI 0.63 to 2.46; Analysis 6.1; I^2 = 77%, 3 studies, N = 627; Figure 4). There was some evidence of a differential impact in the meta-regression analysis (ratio of rate ratios 3.73, 95% CI 0.95 to 14.7, P = 0.057; Table 3). Although univariable meta-regression analysis suggested some association between high coverage of NSP and study design (ratio of rate ratios 3.5, 95% CI 0.78 to 15.8, P = 0.087), this was reduced when adjusted by geographical region (ratio of rate ratios 1.7, 95% CI 0.18 to 16.9, P = 0.58), suggesting any association is confounded by region (Analysis 6.2; Table 3).

2.2 Low-level coverage of NSP versus no NSP coverage

Six studies involving 2763 participants reported adjusted measures of low-level NSP coverage and HCV incidence (Hagan 1995; Hagan 1999; Holtzman 2009; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]). Random-effects meta-analysis showed no evidence of an intervention effect of low NSP coverage on HCV risk acquisition, with moderate levels of heterogeneity (RR 1.43, 95% CI 0.82 to 2.49; Analysis 10.1; I^2 = 69.1%, Tau^2 = 0.272).

Sensitivity analysis

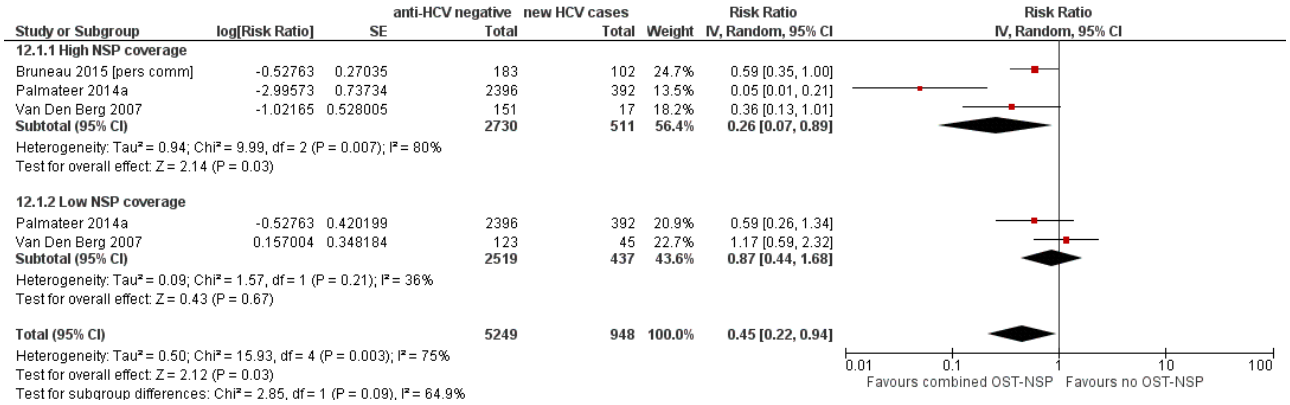
Ten studies reported unadjusted measures of low-level NSP coverage and HCV incidence. Eight were prospective cohorts (Hagan 1999; Holtzman 2009; Maher 2015; Mehta 2015 [pers comm]; Page 2015 [pers comm]; Thorpe 2002; Van Den Berg 2007; White 2014), and one was a case-control study (Hagan 1995). We excluded another prospective cohort study since it did not report 95% confidence intervals around the effect estimate, nor the number of new HCV cases in intervention and comparison groups required to estimate it (Roy 2007). A total of 531 cases were included in the analyses over 1617 person-years. Random-effects meta-analysis showed no evidence of an intervention effect for low NSP coverage on HCV risk acquisition, with moderate levels of heterogeneity (RR 1.41 95% CI 0.95 to 2.09; Analysis 11.1; I^2 = 62.3%, Tau^2 = 0.19, 9 studies, N = 3242).

3. Combined needle syringe programmes plus opioid substitution therapy versus low or no NSP coverage and no OST

Four studies reported combined exposure to both NSPs and OST (Hope 2011; Palmateer 2014a; Van Den Berg 2007) including one unpublished dataset (Bruneau 2015 [pers comm]). The primary analyses focused on three studies presenting adjusted estimates (Bruneau 2015 [pers comm]; Palmateer 2014a; Van Den Berg 2007). A total of 511 HCV incident cases were included in the analysis examining high NSP coverage, and 437 cases for low NSP coverage. Only one study reported the number of person-years (Van Den Berg 2007).

Random-effects meta-analysis showed that combined use of OST plus high coverage of NSP was associated with a 76% risk reduction in HCV acquisition (RR 0.26, 95% CI 0.07 to 0.89; Analysis 12.1; I^2 = 80%, Tau^2 = 0.94; 3 studies, N = 3241; Figure 5). The effect of exposure to OST and low coverage of NSP was weaker (RR 0.87, 95% CI 0.44 to 1.68; Analysis 12.1; I^2 = 36.0%, Tau^2 = 0.09; 2 studies, N = 2956 participants; Figure 5).

Figure 5. Forest plot of comparison: 4 Combined OST and high/low NSP versus no OST and low/no NSP, outcome: 4.1 HCV incidence adjusted analyses.



Sensitivity analysis

Four studies reported unadjusted estimates of combined exposure to both NSPs and OST (Hope 2011; Palmateer 2014a; Van Den Berg 2007) including one unpublished dataset (Bruneau 2015 [pers comm]). Two were cross-sectional surveys (Hope 2011; Palmateer 2014a), and two were prospective cohorts (Bruneau 2015 [pers comm]; Van Den Berg 2007). The analysis examining high NSP coverage included a total of 518 HCV incident cases, and the analysis for low NSP coverage, 449 cases. Random-effects meta-analysis showed that combined use of OST plus high coverage of NSP was associated with a 71% risk reduction in HCV acquisition (RR 0.29, 95% CI 0.13 to 0.65, I^2 = 64.4%, Tau^2 = 0.07, 4 studies, N = 3356). The effect of exposure to OST and low coverage of NSP was weaker (RR 0.76, 95% CI 0.44 to 1.33; Analysis 12.2; I^2 = 29.6%, Tau^2 = 0.4, 3 studies, N = 2956).

DISCUSSION

Summary of main results

Opioid substitution treatment (OST)

Primary meta-analysis of 12 observational studies adjusting for key confounders and enrolling 6361 anti-HCV negative participants showed that current use of opioid substitution therapy reduced the risk of HCV acquisition by 50% (95% CI 37% to 60%) compared to no current OST use. The intervention effect is strong, but the evidence is considered as low quality because it was derived from observational studies with serious risk of bias. Nonetheless, the findings were robust to sensitivity analyses excluding studies judged to be at critical risk of bias; studies drawing on unpublished data; case-control and cross-sectional studies only reporting baseline data; and studies reporting only unadjusted estimates. There was also no evidence of publication bias.

Meta-regression analysis suggested evidence of a differential impact of OST by the proportion of female participants in the sample. With each 10% increase in female participants, the effect of intervention exposure was reduced by 59%. None of the included studies reported uptake of OST by sex to understand whether individual-level analyses supported this evidence of a differential intervention effect. Other epidemiological evidence suggests that women are at increased risk of acquiring hepatitis C compared to men (Esmaeli 2016; Iversen 2015; Miller 2004; Tracy 2014). This increased risk has been linked to having a sexual partner who also injects, being initiated into injection by a sexual partner being injected by others or consistently injecting after other people with used needles/syringes (Bourgois 2004; Iversen 2015). Our findings suggest that women may have poorer access to OST than men, and this is supported by recent review work that suggests services do not take into account gender-specific needs and are often tailored towards men (Iversen 2015).

Only a few studies reported other types of exposure to OST: three studies reported past exposure to OST; three reported interrupted OST use; one study measured OST use for detoxification; and two studies measured high dosage (more than 60 mg) or low dosage (1 to 59 mg) of methadone for daily use. Among these exposures, only high dosage of OST was associated with a reduction in risk of HCV acquisition.

Needle and syringe programmes (NSP)

Meta-analysis of five observational studies pooling adjusted estimates from 3530 anti-HCV negative participants show low-quality evidence that high NSP exposure does not reduce the risk of HCV acquisition. Selected sensitivity analyses increased the uncertainty around the intervention effect. However,meta-regression showed a strong association between intervention effect and region. After removing studies from North America, heterogeneity was reduced, and high NSP coverage in Europe was associated with a 76% (95% CI 38% to 91%) reduction in HCV acquisition risk (RR 0.24, 95% CI 0.09 to 0.62).

Combined NSP and OST

Primary meta-analysis of three studies involving 3241 anti-HCV negative participants and adjusting for confounders suggested a strong intervention effect for combined high coverage of NSP and OST, reducing the risk of HCV acquisition by 74% (95% CI 11% to 93%) compared to no OST and low/no coverage with NSP. The evidence is considered low quality because it was derived from observational studies with serious risk of bias, and the few studies identified precluded sensitivity analyses. Evidence for the combination of low coverage of NSP and OST was weaker. There were fewer studies with information on both OST and NSP coverage, and the studies represented a subset of people on OST (i.e. participants who continue to inject drugs while on OST), with

those on low coverage NSP receiving an insufficient number of sterile syringes per average frequency of injecting.

Overall completeness and applicability of evidence

We found no historical RCT evidence that assessed the impact of NSP or OST on HCV transmission. There was a larger body of observational evidence that examined the effectiveness of NSPs and OST in reducing HCV acquisition among PWID – but the evidence was concentrated in few geographical areas and regions. Most evidence came from North America and Western Europe. Only one study was identified from China (Ruan 2007), and we did not find any studies from Eastern Europe or Southeast Asia, where there are the largest populations of PWID and hence the highest burden of disease associated with bloodborne infections (Gower 2014; Mathers 2008; Platt 2016).

Quality of the evidence

We assessed many studies included in the review as being at severe risk of bias – with only two being at moderate overall risk and seven at critical risk. Only a few studies reported the intervention effect of high NSP coverage adjusting for confounders (5/7), which limited the sensitivity analyses that we could conduct. The GRADE assessment criteria takes RCTs to be the gold standard study design, and observational studies are by default rated as low quality, so the assessment begins low, despite this being the only evidence available for examining this question. While certainty in the results may be undermined by the lack of experimental studies, the intervention effect estimates for current use of OST were consistent and robust across sensitivity analyses, and the size of effect is high. GRADE guidelines also state that judgments about the overall quality of evidence require information beyond the results of the review (GRADE 2004). Considering the wealth of supporting evidence showing the beneficial effects of OST in reducing injecting harms, HIV and bacterial infections, and in improving access to services, we are confident that the assessment is fair (Hagan 2011; MacArthur 2012; Palmateer 2010; Turner 2011; Vickerman 2012; Vickerman 2014).

Potential biases in the review process

A potential bias in the review was the heterogeneity across the studies in the use of multiple effect measures. Effect measures were converted into risk ratios in the meta-analysis, but this may have introduced bias into our findings since we had to assume that risk ratios approximated odds ratios, which may be inappropriate for some sites given the high incidence of HCV seroconversion. We removed cross-sectional study designs that identified serological markers of incidence infection as part of our sensitivity analysis. Effect estimates remained the same for current use of OST versus no intervention, but not for high coverage of NSPs. Nonetheless, most studies recruited people who inject drugs currently or recently, which may not be representative of all PWID exposed to OST and may lead to an underestimation of the effect of OST on HCV transmission. For example, in the Amsterdam cohort, people who reported being on OST and having ceased injecting had a lower risk of HCV transmssion (Van Den Berg 2007). Another potential bias is the use in three studies of HCV RNA testing for anti-HCV negative samples to obtain an estimate of incidence (Hope 2011; Hope 2015 [pers comm]; Palmateer 2014a). Potential limitations of this method include delayed or weak antibody response due to a compromised immune system and uncertainty around the incidence window period (Hope 2010). All included studies estimating incidence from RNA samples used the same formula and comparable window periods. We didn't include any studies that used avidity testing, minimising any further misclassification of outcomes that that approach brings through the uncertainty in window periods.

Agreements and disagreements with other studies or reviews

Our review corroborates and underpins an earlier review that showed consistent and large effects of NSP and OST on injecting risk behaviours associated with bloodborne virus transmission (Gowing 2011). Two recent reviews focused on the effectiveness of OST and NSPs in reducing HCV incidence. Our findings corroborate the most recent pooled analysis, which suggested that receiving OST and high coverage of NSP can each reduce HCV infection risk alone but have a greater effect in combination (Turner 2011). The estimate for association between exposure to NSP and HCV incidence was weak in the pooled analysis and was focused on studies from the UK only. Findings from our subgroup analysis suggested a stronger effect of high NSP coverage in Europe. This finding builds directly on the Turner 2011 analysis through the addition to the meta-analysis of the earlier Van Den Berg 2007 along with more recent studies and datasets (Hope 2015 [pers comm]), and it strengthens the efficacy estimate for Europe suggesting reduced risk of HCV acquisition (RR 0.24 95% CI 0.09 to 0.62). We found no effect of high NSP coverage when pooling estimates from North America and greater heterogeneity across the studies. This corroborates findings from another review that found increased risk of seroconversion associated with NSP attendance that relied on evidence predominantly from North America (Hagan 2011).

The lack of evidence for NSPs from studies in North America can be attributed to a mixture of confounding, differences in injecting patterns, potential selection bias and misclassification of exposure. People who attend NSPs regularly also report greater injecting risk behaviours, and any positive association between HCV transmission and NSP attendance disappears after adjustment for injecting risk. The effect of this residual confounding has been demonstrated in further analyses of a cohort of PWID in Vancouver, which demonstrated that higher HIV seroconversion rates observed among daily NSP attenders were associated with high-risk behaviours of attenders (including regular cocaine injection, sex work involvement and homelessness) rather than use of the NSP (Wood 2007). Likewise, a study in Seattle showed that people who were homeless or who injected with used needle/syringes were more likely to become new NSP users (Hagan 2000). The higher proportion of stimulant injecting in North America also means that the additional protective effect of OST is absent, which may contribute to the impact of NSP on HCV risk in European studies. Potential selection bias may occur since samples of cohort studies are to some degree self-selected. Particularly when participants are lost to follow-up over time, they may be inherently different in terms of demographic characteristics and risk behaviours that can influence the outcome. Misclassification of exposure may also occur since it is difficult to make a clear distinction between exposed and unexposed groups, and unexposed populations may have access to clean needles/syringes through other sources than NSPs. The European studies consistently used measures of NSP exposure through coverage of injections by clean needles/syringes, whereas the North American

studies drew on varied definitions of NSP use that focused on frequency of attendance at NSPs. Comparability in measurement of intervention exposure is reflected in the higher heterogeneity observed among studies measuring exposure to NSP (I^2 = 77%, P = 0.002) compared to OST exposure (I^2 = 0%, P = 0.89). This is particularly relevant in relation to measures of intervention exposure that focus on frequency of attendance at an NSP rather than a measure of injections covered by clean needle/syringes, and further explains the lack of effect between high NSP coverage and HCV incidence observed in North America. It is also possible that the lack of effect of NSPs on HCV transmission observed in North America is due to less frequent use of NSPs. Previous evidence has shown that lack of federal funding for NSPs in the USA has resulted in lower coverage among PWID, and this has been associated with higher HIV incidence than in other countries with higher NSP coverage (Wiessing 2009).

Findings also corroborate two recent systematic reviews that measured the impact of NSPs and OST on HIV transmission. These previous analyses of 12 observational studies estimated a moderate effect of NSPs on reducing HIV transmission by 48% (95% CI 3% to 72%) and strong evidence for OST reducing HIV transmission by 54% (95% CI 33% to 68%) (Aspinall 2014; MacArthur 2012).

A previous review of reviews from 2010 concluded that there was insufficient evidence to assess the effectiveness of NSPs in reducing HCV incidence. This 'meta' review synthesised findings from four primary reviews, three of which focused primarily on HIV as an outcome, missing much of the relevant data, and the fourth predominantly relied on weaker study designs (Palmateer 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Opioid substitution treatment (OST) reduces the risk of HCV acquisition in PWID. The evidence for the effectiveness of high coverage needle syringe programmes (NSP) was more mixed – with evidence from studies in Europe suggesting that NSP reduce HCV transmission, but not in the USA, probably due to misclassification of intervention exposure, selection bias of study participants and unmeasured bias. The intervention effect is strengthened with the combination of OST and high coverage NSP. The World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS, the United Nations Office on Drugs and Crime, the European Centre for Disease Prevention and Control, and the European Monitoring Centre for Drugs and Drug Addiction all recommend OST and NSPs as key interventions for preventing drug-related harm, including HCV transmission. Yet OST is not widely implemented in many countries, prohibited in the Russian Federation and often restricted by age or duration of dependency prior to treatment entry (Mathers 2012).

Our findings show the need to remove restrictions on the concurrent use of both NSP and OST to maximise reduction in HCV transmission. Distribution of needles/syringes through NSPs needs to be maintained alongside provision of OST. NSP and OST services need to recognise the role of gender and develop appropriate policies and practice to encourage women to use services addressing the specific injecting-related risk behaviours they face and addressing other health and social welfare needs. We only identified three studies that examined effectiveness of interrupted use of OST, but effectiveness was reduced. Similarly, available evidence to examine differences in effect by dosage was limited.

Implications for research

There is low-quality evidence demonstrating the effectiveness of OST for reducing risk behaviour and transmission of HCV and HIV. However, there is a need to understand the role of duration of OST use in reducing the risk of both HIV and HCV. For NSPs, evidence needs to be strengthened. There is a need for more consistent measurement in the coverage of NSPs across epidemiological studies to obtain better effect estimates for NSPs as well as understanding how injection of stimulants or prescription opioids changes their effectiveness. There is a need for better studies on NSP impact in North America and for combining studies on OST and NSP implementation and roll-out and effect on HCV transmission in general in low- and middle-income countries. Given the body of observational evidence on effect of OST and NSP on reducing HIV, HCV incidence and other injecting related harms, it is not ethical to individually randomise exposure to OST or NSP, so future trial evidence can only be derived from cluster-randomised controlled trials or stepped wedge design. Current guidance means that the quality of the evidence will typically be assessed as low.

Research direction also needs to turn to implementation and understanding how NSPs and OST can be scaled up and delivered more effectively to better respond to the health needs of PWID, which requires observational study designs. We know that effectiveness of NSP varies by geographical location, but without the provision of counselling (psychosocial and voluntary counselling and testing for HIV and HCV), education and drug treatment services like opioid substitution therapy, NSPs are insufficient to reduce epidemics of HIV and HCV in PWID (Strathdee 1997; Vickerman 2012). More detailed assessments should examine service delivery and their cost-effectiveness in order to ensure existing services are maintained and to promote the introduction and scale-up of services in countries and settings with emerging or growing epidemics of injecting and opioid drug use. This line of research can shed light on the pathways between contextual factors and mechanisms of service delivery, and the extent to which these influence effectiveness across different outcomes. For example, HIV and HCV epidemics continue unchecked in Eastern Europe despite implemention of OST and NSP in some countries (Vickerman 2014). Epidemics are growing in countries in sub-Saharan Africa, including Tanzania and Kenya, where OST is currently being implemented, but there has been little formal evaluation of different models of delivery; specific economic, social and political contexts; and the impact of specific epidemiology of HIV and HCV. Further, we identified only one study conducted in a middle-income country (China) and no studies in low-income countries. There was insufficient evidence to examine differences in effectiveness by NSP modality or setting of OST. This reflects a lack of evaluation of provision of OST or NSP in other settings. Further research is needed to examine how the effect of NSP differs by service modality, including pharmacies, mobile clinics or outreach services. Similarly, research into the effectiveness of OST delivered in specialist services, community settings and prisons is needed.

While evidence for the combined effect of OST and high NSP coverage is stronger, we only identified four studies, and only three of those adjusted for confounders. Further evidence is needed to understand how effectiveness may differ by modality,

duration of OST as well as impact on other health outcomes associated with injecting drug use, including bacterial infections and mental health, among others. Given the low quality of evidence, there is a need to improve transparency and consistency in reporting of observational studies to facilitate systematic reviews of observational studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aitken 2015 [pers comm]

Methods	Prospective cohort study; recruitment was done via RDS, street outreach and snowball sampling
Participants	Country: Australia 449 PWID, defined as 'regularly' injecting illicit drugs in the last 6 months. Median age was 29.4 years, and 50% of participants reported injecting daily, but there was no information on the main drug being injected.
Interventions	The intervention in this study was use of opioid substitution therapy (OST); OST was defined as use of OST in the previous month. The comparison group was no current OST use. Follow-up: 196 person years Study duration: 5 years
Outcomes	HCV seroconversion as measured by HCV antibody in serum
Notes	Funding source is the Australian National Health and Medical Research Council

Bruneau 2015 [pers comm]

Methods	Prospective cohort study; recruitment was done via street outreach, and snowball sampling
Participants	Country: Canada 285 PWID
Interventions	The interventions included in this study were needle syringe exchange programme (NSP) use in the previous 3 or 6 months, use of methadone maintenance in the previous 6 months. Further detail on the intensity of engagement with the intervention was gathered; researchers examined NSP use where 100% of needles/syringes used were obtained by NSP and a methadone dose of 0-60 mg or 60+ mg, respectively. Comparisons were no NSP use in the previous 3 or 6 months or low NSP coverage (< 100%), no OST use in the previous 6 months, or < 59 mg of methadone Follow-up: 589.3 person years Study duration: 7 years
Outcomes	HCV seroconversion
Notes	The funding source was the Canadian Institutes of Health Research, US National Institute on Drug Abuse and the Réseau SIDA et Maladies Infectieuses du Fonds de la Recherche en Sante du Quebec

Craine 2009

Methods	Prospective cohort study
Participants	Country: Wales, UK 700 PWID, defined as injecting drugs in the previous 4 weeks. 29% were female and the mean age was 27.2 years. The main drug injected was not reported, but 42% had injected stimulants.
Interventions	The intervention was either in opioid substitution treatment or not Follow-up: 287.3 person years

Craine 2009 *(Continued)*

	Study duration: 2 years
Outcomes	HCV seroconversion
Notes	Funded by the Welsh Assembly Government

Crofts 1997

Methods	Retrospective cohort study
Participants	Country: Australia 1741 PWID; the mean age was 29.2 years and 42% were female; main drug was not reported
Interventions	The intervention was defined as either continuous or interrupted methadone maintenance treatment; the comparison was no methadone maintenance Follow-up: 85.4 person years Study duration: 4 years
Outcomes	HCV seroconversion
Notes	Individual funding was received from Research Fund of the Macfarlane Burnet Centre, Victorian Department of Health and Community Services Public Health Training Programme, the Commonwealth Department of Health and Family Service.

Hagan 1995

Methods	Case-control study
Participants	Country: USA 46 PWID, where PWID status was defined as having injected drugs in the previous 6 months (cases). 24% of the sample were < 25 years, 45% were female; the main drug injected was not reported
Interventions	The intervention under study was ever having used a needle syringe exchange programme and comparison was never having used a NSP Follow-up: n/a Study duration: 2 years
Outcomes	HCV seroconversion defined by presence of HCV antibodies
Notes	Funded by the American Foundation for AIDS Research

Hagan 1999

Methods	Prospective cohort study
Participants	Country: USA

Hagan 1999 *(Continued)*

	2462 PWID, defined as having injected drugs in the previous 12 months. 19% were < 25 years, 38% were female, 54% injected heroin and 59% injected daily
Interventions	The intervention under study was either current sporadic or current regular needle syringe exchange programme use; the comparison was no use of the NSP. Follow-up: 209 person years Study duration: 2 years
Outcomes	HCV seroconversion defined by presence of HCV antibodies (the timeframe for seroconversion was within the previous 12 months)
Notes	Funded by the National Institute on Drug Abuse and Centre for Disease Control

Holtzman 2009

Methods	Prospective cohort study; recruitment was done via RDS and street outreach
Participants	Country: USA 4663 PWID, defined as injecting drugs in the previous 6 or 12 months. 28% were less than 21 years old, 38% were female; main drug injected was not reported, but 49% injected daily
Interventions	The intervention was participation (yes/no) in a needle syringe exchange programme (NSP) in either the previous 3 months or 6 months Follow-up: n/a Study duration: 10 years
Outcomes	HCV seroconversion measured by the presence of HCV antibodies
Notes	Funding source not specified

Hope 2011

Methods	Cross-sectional study. Recruitment of study participants was done via RDS
Participants	Country: England, UK 299 PWID, defined as having injected drugs in the previous 4 weeks. 17% were < 25 years old, 23% were female, 94% injected opiates, 40% injected daily
Interventions	The interventions were as follows: 1. Low NSP coverage and not on OST 2. Low NSP coverage and OST 3. High NSP coverage and no OST 4. High NSP coverage and OST Comparisons were no current use of OST, no or low NSP coverage Follow-up: n/a

Hope 2011 *(Continued)*

	Study duration: 6 months
Outcomes	HCV seroconversion defined as HCV RNA positive and HCV antibody negative (dried blood spot testing); the window period for the outcome was 51–75 days (range)
Notes	Funded by the National Treatment Agency for Substance Use and Health Protection Agency

Hope 2015 [pers comm]

Methods	Cross-sectional study; recruitment of study participants was done via RDS
Participants	Country: England, UK 948PWID, defined as having injected drugs in the previous 4 weeks. Median age was 33 years, 48% injected heroin as their main drug, but 64% had injected crack/cocaine in the previous month, 19% were female and 53% injected daily
Interventions	The interventions were as follows: 1. Low NSP coverage and not on opioid substitution treatment OST 2. Low NSP coverage and OST 3. High NSP coverage and no OST 4. High NSP coverage and OST Comparisons were no current use of OST, no or low NSP coverage Follow-up: 6 months
Outcomes	HCV seroconversion defined as HCV RNA positive and HCV antibody negative (dried blood spot testing); the window period for the outcome was 51–75 days (range) Follow-up: n/a Study duration: 6 months
Notes	Funded by National Treatment Agency for Substance Use and the Health Protection Agency

Judd 2015 [pers comm]

Methods	Prospective cohort study; recruitment was conducted via privileged access interviews and snowball sampling
Participants	Country: England, UK 272 PWID, defined as having injected drugs in the previous 4 weeks. Median age was 27.6 years, 29% were female, 35% mainly injecting heroin, 84% injected daily
Interventions	The intervention of interest was use of methadone maintenance treatment in the previous 6 months or longer, compared to no methadone in the same time period Follow-up:116.7 person years Study duration: 2 years
Outcomes	HCV seroconversion

Judd 2015 [pers comm] *(Continued)*

Notes	Funded by the UK Department of Health

Lucidarme 2004

Methods	Prospective cohort study; recuitment was conducted at drug treatment centres
Participants	Country: France 321 PWID, defined as ever having injected drugs. Median age was 26.9 years, 17.6% were female, 28% injected opiates, 84% injected daily
Interventions	The intervention under study was having received OST in the 3 months prior to study enrollment; the comparison was no OST in the 3 months prior to study enrollment Follow-up: 178.4 person years Study duration: 1 year
Outcomes	Seroconversion measured as the presence of HCV antibodies in oral fluid and serum on positive tests; the window period for the outcome was the midpoint between previous negative oral fluid test and first positive serum test
Notes	Funded by the Agence Nationale de Recherche su le SIDA, Institute de Veille Sanitaire, Programme Hospitalier de Recherce Clinique, Direction Departementale de l'Action Sanitaire et Sociale du Nord, Academie Nationale de Medecine

Maher 2015

Methods	Prospective cohort study; recruitment was conducted in community settings and in low-threshold drug treatment settings
Participants	Country: Australia 294 PWID, defined as injection in the previous 6 months. Median age was 24 years, 32% were female, 69% injected heroin
Interventions	The intervention under study was having received OST in the previous 6 months; the comparison was no OST in the previous 6 months Follow-up: 212.86 person years Study duration: 3 years
Outcomes	Seroconversion as measured by anti-HCV serology at baseline using 1-2 third-generation enzyme-linked immunosorbent assays. PCR testing to detect HCV RNA on all final HCV antibody negative specimens
Notes	Funded by the Australian National Health and Medical Research Council

Mehta 2015 [pers comm]

Methods	Prospective cohort study; recruitment was conducted through community-based outreach

Mehta 2015 [pers comm] *(Continued)*

Participants	Country: USA 471 PWID, defined as having injected within the preceding 11 years. Median age was 34 years, 18.3% were female, 65% injected heroin and cocaine, 92% had injected in the previous year at baseline
Interventions	The intervention under study was being in methadone treatment in the previous 6 months; the comparison was no methadone treatment in the previous 6 months Follow-up: 166.5 person years Study duration: 20 years
Outcomes	HCV seroconversion, measured through serum samples
Notes	Funded by the National Institute on Drug Abuse

Nolan 2014

Methods	Prospective cohort study; recruitment included snowball sampling
Participants	Country: Canada 3741 PWID, defined as having injected drugs in the previous 4 weeks. 30% were female, 34% injected opiates and the mean age was 34 years among methadone users and 23 years among non-methadone users
Interventions	The interventions under study were: 1. Active participation in methadone maintenance treatment (MMT) in last 6 months 2. MMT once during follow-up, 3. MMT > 2 times during follow-up Comparison was no use of MMT within the same time periods Follow-up: 2108.4 person years Study duration: 16 years
Outcomes	HCV seroconversion defined by presence of HCV antibodies
Notes	Funded by the US National Institutes on Drug Abuse

Page 2015 [pers comm]

Methods	Prospective cohort study; recruitment occurred through street outreach
Participants	Country: USA 552 PWID, defined as people who have injected drugs in the previous month and less than 30 years old. 42.5% were < 22 years, 22% were female and 61% injected heroin/heroin mixed in the previous month
Interventions	The intervention under study was use of a NSP in the previous 3 months and the comparison was no use of NSP Follow-up: 681.3 person years

Page 2015 [pers comm] *(Continued)*

	Study duration: 15 years
Outcomes	HCV seroconversion defined by presence of HCV antibodies or HCV RNA
Notes	Funded by the National Institute on Drug Abuse

Palmateer 2014a

Methods	Cross-sectional study; participants were recruited at NSPs
Participants	Country: Scotland, UK 7954 PWID, defined as ever having injected drugs (but 80% had injected in previous 6 months). Mean age is 34 years, 27.5% are female, 55.3% inject daily and 17% injected stimulants
Interventions	The interventions were defined as: 1. Needle syringe exchange (NSP) coverage: low vs high 2. Paraphernalia coverage: low vs high 3. Opioid substitution treatment (OST): current vs not current 4. NSP and OST combined: low NSP, no OST vs low NSP with OST, high NSP no OST, high NSP OST, did not inject OST 5. NSP, paraphernalia, and OST combined: low NSP, low para, no OST vs low NSP, low para with OST, high NSP, low para, no OST, high NSP, low para, OST, high NSP, high para, no OST, high NSP, high para, OST, did not inject OST The comparisons were no OST or no/low NSP use Follow-up: 602.7 person years Study duration: 4 years
Outcomes	The outcome was HCV seroconversion defined as being HCV antibody negative and HCV RNA positive
Notes	Funded by the Scottish Government

Patrick 2001

Methods	Prospective cohort study; recruitment included snowball sampling
Participants	Country: Canada 1345 PWID, defined as having injected drugs in the previous 4 weeks. 30% were female, the median age was 34 years, 63% injected opiates and 54% injected stimulants, 54% injected daily
Interventions	The intervention under study was 1. Attendance at least once per week at NSP in previous 6 months (yes or no) 2. Methadone maintenance treatment in previous 6 months (yes or no) The comparison was NSP attendance or no methadone in the previous 6 months Follow-up: 207.9 person years Study duration: 3 years

Patrick 2001 *(Continued)*

Outcomes	HCV seroconversion measured by HCV antibody positivity
Notes	Funding source was not specified

Rezza 1996

Methods	Case-control study; recruitment methods employed a convenience sample of service attenders
Participants	Country: Italy 746 PWID, defined as being a heroin user. 21% were < 28 years, 3% were female, 100% injected opiates and 32% also injected stimulants, 69% injected daily
Interventions	The intervention under study was being in methadone maintenance treatment in the previous 6 months, the comparison was no methadone maintenance in the same time period Follow-up: 73.4 person years Study duration: 2 years
Outcomes	HCV seroconversion, measured by HCV antibody positivity in serum samples
Notes	Funded by the Progretto AIDS, Ministero della Sanita-Instituto Superiore di Sanita

Roy 2007

Methods	Serial cross-sectional survey; recruitment methods employed service attenders at drug treatment programmes
Participants	Country: Canada 1380 PWID, defined as having injected in the previous 6 months. Mean age was 31.8 years, 27% were female, 19% injected opiates and 75% injected stimulants
Interventions	The intervention under study was using an NSP in the previous 6 months, and the comparison was no use of the NSP Follow-up: 267 person years Study duration: 6 years
Outcomes	HCV RNA positive on anti-HCV negative (oral fluid). HCV seroconversions were attributed to the midpoint between the previous negative and first positive test results
Notes	Funded by the Health Canada, Ministere de la Sante et des Services Sociaux du Quebec

Ruan 2007

Methods	Prospective cohort study; recruitment occurred via community outreach and snowball sampling
Participants	Country: China

Ruan 2007 *(Continued)*

	379 PWID, defined as having injected drugs in the previous 3 months. 44% were < 28 years and 100% injected opiates. There was no information on sex or frequency of injecting.
Interventions	The intervention of interest was lifetime experience of methadone maintenance treatment (yes or no). Follow-up: 258 person years Study duration: 3 years
Outcomes	HCV antibody positivity in serum samples (incidence density); the time of seroconversion was the midpoint between the previous negative and first positive HCV antibody test result
Notes	Funded by the Ministry of Science and Technology of China, the National Natural Science Foundation of China, China Comprehensive Integrated Programmes for Research on AIDS, the National Institute of Allergy and Infectious Diseases and the National Institutes of Health

Spittal 2012

Methods	Prospective cohort study; recruitment via community outreach and snowball sampling
Participants	Country: Canada 377 PWID, defined as having injected in the previous 4 weeks. Median age was 23 years, 53% were female, 18% injected opiates, 10% injected stimulants, 18% injected daily
Interventions	The intervention of interest was being in methadone maintenance treatment (yes or no) at the time of survey; comparison was no current use of methadone maintenance Follow-up:338.6 person years Study duration: 6 years
Outcomes	HCV antibody positivity in serum samples (incidence density); the time of seroconversion was the midpoint between the previous negative and first positive HCV antibody test result
Notes	Funded by the Institute for Aboriginal Peoples Health and the Canadian Institutes for Health Research

Thiede 2000

Methods	Prospective cohort study; recruitment from a drug treatment setting
Participants	Country: USA 716 PWID, defined as having injected drugs in the previous 4 weeks. 5.4% were < 25 years, 49% were female, 23% injected stimulants and 25% injected daily
Interventions	The interventions under study were: 1. Left methadone maintenance treatment (MMT) at least once during follow-up but were re-enrolled at their follow-up visit 2. Remained in MMT throughout the follow-up period The comparison was no MMT. Follow-up: 80 person years

Thiede 2000 *(Continued)*

	Study duration: 4 years
Outcomes	HCV seroconversion, as demonstrated by the presence of HCV antibodies in serum
Notes	Funded by the Centers for Disease Control and Prevention

Thorpe 2002

Methods	Prospective cohort study; recruitment via street outreach, targeted advertising, and peer referrals
Participants	Country: USA 702 PWID, defined as having injected in the previous 6 months. 53% were aged 18-22 years, 49% were female, 23% injected stimulants and 39% injected daily
Interventions	The intervention of interest was use of an NSP in the previous 6 months and the comparison was no use of the NSP Follow-up: 327.2 person years Study duration: 2 years
Outcomes	HCV seroconversion as demonstrated by the presence of HCV antibodies in serum; time of seroconversion was taken to be the midpoint between the previous negative and first positive HCV antibody test result
Notes	Funding source was not specified

Tsui 2014

Methods	Prospective cohort study; recruitment via street outreach
Participants	Country: USA 992 PWID, defined as having injected in the previous 4 weeks and aged < 30 years. 16% were aged 15-18 years, 32% were female, 60% injected opiates and 33.2% injected stimulants
Interventions	The interventions of interest included: 1. Opiate agonist detoxification in previous 3 months 2. Opiate agonist therapy maintenance treatment in previous 3 months. Recent opioid agonist therapy included treatment with buprenorphine or methadone anytime within the past year at the baseline screening interview, within the past 3 months at quarterly interviews for participants in waves 1 and 3, and within the past week for participants in wave 2 The comparison was no opiate agonist therapy in the same time frame Follow-up: 680 person years Study duration: 13 years
Outcomes	HCV seroconversion. Incidence was calculated using behavior or characteristic at the previous period that participant was seronegative for HCV (uninfected during follow-up) or the first HCV-seropositive risk period (incident infections). Incident acute HCV infections were: a new test result positive for HCV

Tsui 2014 *(Continued)*

	RNA and/or anti-HCV after a previously documented test result negative for anti-HCV; or a positive HCV RNA test result concomitant with a negative anti-HCV test result.
Notes	Funded by the National Institute on Drug Abuse, National Institute of Health, National Institute on Alcohol and Alcoholism

Vallejo 2015

Methods	Prospective cohort study; recruitment was street-based and employed targeted sampling and chain-referral methods
Participants	Country: Spain 513 PWID; PWID were required to have used heroin at least 12 days and at least 1 day in the past 3 months. 40% were < 25 years, 27% were female, 31% injected stimulants. There was no information on daily injecting.
Interventions	The intervention of interest was methadone maintenance; further details of the intervention (e.g. intensity or duration of engagement in the intervention) was not specified, the comparison was no use of methadone maintenance. Follow-up: 105.4 peron years Study duration: 3 years
Outcomes	HCV seroconversion, defined by HCV antibody positivity by dried blood spot testing
Notes	Funded by the Foundation for AIDS Prevention and Research

Van Beek 1998

Methods	Retrospective cohort study; recruitment at drug treatment services
Participants	Country: Australia 1078 PWID, 61.5% were < 20 years, 55.9% were female, 19% injected opiates, 27.9% injected stimulants
Interventions	The intervention under study was ever having received methadone; the comparison was no methadone Follow-up:148.2 person years Study duration: 2 years
Outcomes	HCV seroconversion
Notes	Funded by the Australian National Council on AIDS and Related Diseases

Van Den Berg 2007

Methods	Prospective cohort study; enrollment occurred through 'open' recruitment
Participants	Country: Netherlands

Van Den Berg 2007 *(Continued)*

	168 PWID, defined as those who had ever injected drugs. Median age was 31.4 years, 33% were female, 33% injected opiates and 51% injected stimulants, 51.7% injected daily
Interventions	The interventions of interest were measured as follows: 1. Incomplete harm reduction: any dose of methadone daily, injection in previous 6 months, irregular or no use of NSP; OR 0-59 mg of methadone daily in past 6 months, always use NSP 2. Full harm reduction: ≥ 60 mg of methadone daily in past 6 months; no injecting drug use; ≥ 60 mg methadone daily, injecting drug use in past 6 months, always use NSP 3. Limited dependence on harm reduction: 1-59 mg of methadone in past 6 months, no injecting drug use 4. No dependence on harm reduction: no methadone in in past 6 months, no injection in past 6 months. The comparsion was no methadone in the past 6 months, and/or no use of NSP or no injection Follow-up: 598.56 person years Study duration: 22 years
Outcomes	HCV seroconversion
Notes	Funded by the Netherlands National Institute for Public Health and the Environment

White 2014

Methods	Prospective cohort study; recruitment via snowball sampling, social networks, RDS, and targeted outreach sampling
Participants	Country: Australia 166 PWID, defined as those who had injected drugs in the previous 12 months. Median age was 27 years, 25% were female. Participants mainly injecting opioids, but frequency of injecting was not reported
Interventions	The intervention assessed was having accessed a needle syringe exchange programme or opioid substitution treatment in the previous 6 months, the comparison was no use of the NSP or OST in the same time frame. Follow-up: 215.2 person years. Study duration: 3 years
Outcomes	HCV seroconversion defined as being negative for HCV antibodies and positive for HCV RNA
Notes	Funded by the National Health and Medical Research Council

HCV: hepatitis C virus; **NSP**: needle syringe programme; **OST**: opioid substitution therapy; **PCR**: polymerase chain reaction; **PWID**: people who inject drugs; **RDS**: respondent-driven sampling.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aubisson 2006	No outcome of interest
Azim 2005	No outcome of interest

Study	Reason for exclusion
Bayoumi 2008	No intervention of interest: no OST or NSP
Burt 2007	No outcome of interest
Buxton 2010	No outcome of interest; no comparison of interest: all participants on OST
Collins 2009	No outcome of interest
Cox 2000	No outcome of interest
Crofts 1993	No intervention of interest: no OST or NSP
De Vos 2012	No outcome of interest; simulation study
Des Jarlais 2005	No outcome of interest
Des Jarlais 2007	No outcome of interest
Dubois-Arber 2008	No outcome of interest
Emmanuelli 2005	No outcome of interest
Esteban 2003	No outcome of interest. No comparison of interest: all participants on OST
Falster 2009	No outcome of interest
Fatseas 2012	No outcome of interest
Fhima 2001	No comparison of interest: all participants on OST
Fudala 2003	No outcome of interest
Fuller 2004	No intervention of interest: no OST or NSP
Galeazzl 1995	No outcome of interest; no intervention of interest: no OST or NSP
Gambashidze 2008	No outcome of interest
Garfein 1998	No outcome of interest; no intervention of interest: no OST or NSP
Garfein 2007	No outcome of interest; no intervention of interest: no OST or NSP
Garten 2004	No intervention of interest: no OST or NSP
Gervasoni 2012	No outcome of interest
Goldberg 1998	No outcome of interest
Goldberg 2001	No outcome of interest
Goswami 2014	No outcome of interest
Grebely 2013	Editorial
Grebely 2014	No intervention of interest: no OST or NSP

Study	Reason for exclusion
Guadagnino 1995	No outcome of interest; No intervention of interest: no OST or NSP
Hagan 2000	No outcome of interest; no intervention of interest: no OST or NSP
Heimer 1999	No outcome of interest
Higgs 2012	No outcome of interest
Jackson 2014	No comparison of interest: all participants on OST
Javanbakht 2014	No outcome of interest; simulation study
Judd 2005	No intervention of interest: no OST or NSP
Kwon 2009	No outcome of interest; simulation study
Lai 2001	No intervention of interest: no OST or NSP
Larney 2015	No comparison of interest
Mansson 2000	No outcome of interest
Mikolajczyk 2013	No intervention of interest: no OST or NSP
Moshkovich 2000	No outcome of interest
Muga 2006	No outcome of interest
Nasir 2011	No outcome of interest
Page 2009	No intervention of interest: no OST or NSP
Page 2013	No intervention of interest: no OST or NSP
Palmateer 2014b	No intervention of interest: no OST or NSP
Paquette 2010	No intervention of interest: no OST or NSP
Parrino 2003	Overview
Pedrana 2009	No intervention of interest: no OST or NSP
Peles 2011	No comparison of interest: all on OST
Pollack 2001	No outcome of interest; simulation model
Pratt 2002	No outcome of interest
Robotin 2004	No intervention of interest: no OST or NSP
Rohrig 1990	No outcome of interest
Roux 2012	No outcome of interest. No comparison of interest: all participants on OST
Roux 2014	No outcome of interest

Study	Reason for exclusion
Roy 2009	No intervention of interest: no OST or NSP
Roy 2012	No intervention of interest: no OST or NSP
Ruan 2013	No intervention of interest: no OST or NSP
Samo 2013	No outcome of interest
Sanders-Buell 2013	No outcome of interest
Seal 2004	No outcome of interest
Selvey 1997	No comparison of interest: all participants on OST
Sendi 2003	No intervention of interest: no OST or NSP
Shannon 2010	No intervention of interest: no OST or NSP
Shi 2007	No comparison of interest: all participants on OST
Solomon 2010	No intervention of interest: no OST or NSP
Spencer 1997	No intervention of interest: no OST or NSP
Steffen 2001	No intervention of interest: no OST or NSP
Stein 2009	No intervention of interest: no OST or NSP
Stephens 2011	No outcome of interest. No intervention of interest: no OST or NSP
Stephens 2013	No intervention of interest: no OST or NSP
Strathdee 1997	No outcome of interest
Sullivan 2005	No outcome of interest. No comparison of interest: all participants on OST
Sylvestre 2006	No outcome of interest
Tait 2013a	No outcome of interest. No intervention of interest: no OST or NSP
Tait 2013b	No outcome of interest. No intervention of interest: no OST or NSP
Todd 2015	No intervention of interest (NSP shuts down for some of the follow-up)
Tracy 2014	No intervention of interest: no OST or NSP
Tsirogianni 2013	No intervention of interest: no OST or NSP
Tsui 2009	No intervention of interest: no OST or NSP
Valdez 2011	No outcome of interest. No intervention of interest: no OST or NSP
Van Ameijden 1993	No intervention of interest: no OST or NSP
Van den Hoek 1990	No outcome of interest

Study	Reason for exclusion
Van den Laar 2009	No outcome of interest. No intervention of interest: no OST or NSP
Van den Laar 2010	No outcome of interest. No intervention of interest: no OST or NSP
Van Santen 2013	No outcome of interest
Villano 1997	No intervention of interest: no OST or NSP
Wand 2009	No intervention of interest: doesn't specify OST, only that it is drug treatment
Wang 2014	No comparison of interest: all participants on OST
Widell 2009	No intervention of interest: no OST or NSP
Winkelstein 2013	No outcome of interest
Woody 2008	No outcome of interest
Yang 2011	No outcome of interest
Yen 2012	No outcome of interest
Zhao 2005	No outcome of interest
Zhou 2015	No comparison of interest: all participants on OST
Zou 2015	No comparison of interest: all participants on OST
Zunt 2006	No outcome of interest

NSP: needle syringe programme; OST: opioid substitution therapy.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bruneau 2016

Methods	Prospective cohort
Participants	313 HCV-seronegative PWID (injection in the previous month) were enrolled with at least one follow-up visit. 22% were female, 43% were under 30 years old and 58% injected cocaine
Interventions	Opioid agonist therapy (1-59 mg, methadone or suboxone, ≥ 60 mg methadone) and injection material coverage (100% safe sources vs no)
Outcomes	Seroconversion to HCV antibody positive
Notes	The study was conducted in Montreal, Canada. No funding source is specified.

Chun 2006

Methods	—

Chun 2006 *(Continued)*

Participants	—
Interventions	—
Outcomes	—
Notes	There is no abstract, and the text is in Chinese.

Duan 2013

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	There is no abstract, and the text is in Chinese.

He 2003

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	There is no abstract, and the text is in Chinese.

He 2004

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	There is no abstract, and the text is in Chinese.

Mathei 2016

Methods	—

Mathei 2016 *(Continued)*

Participants	—
Interventions	—
Outcomes	—
Notes	The text is in French, and there is little information in the abstract.

O'Keefe 2016

Methods	Prospective cohort recruited between 2011 and 2015
Participants	People who inject drugs, defined as regular injectors (at least one a month in the 6 months prior to recruitment), a total of 502 participants, approximately 36% were female and mean age 30 was years
Interventions	Current opoid substitution therapy prescription; NSP as usual source of syringe acquisition in the past month, measure of injections covered by sterile syringe (syringes acquired divided by syringes distributed divided by past week injecting frequency)
Outcomes	HCV RNA positive among negative samples
Notes	Data drawn from the Melbourne injecting drug use cohort study (MIX). Funding provided by the Colonial Foundation Trust and the National Reserch Council

Ray Saraswati 2015

Methods	Longitudinal incidence study, participants recruited in community settings through peer referrals in places where drugs are used
Participants	People who inject drugs defined as injection at least once in the previous 3 months and residing in Delhi. A total of 2292 PWID recruited of whom all were male; median age was 29 years
Interventions	Accessed NSP in the previous 3 months
Outcomes	anti HCV negative and HCV RNA positive
Notes	Funding received from the Canadian Government (Department of Foreign Affairs, Trade and Development Canada). No incidence data reported, but need to contact authors for measures

Siedentopf 2002

Methods	—
Participants	—
Interventions	—
Outcomes	—

Siedentopf 2002 *(Continued)*

Notes	There is no abstract, and the text is in German.

Wada 2004

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	There is no abstract, and the text is in Japanese.

HCV: hepatitis C virus; **NSP**: needle syringe programme; **PWID**: people who inject drugs.

DATA AND ANALYSES

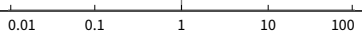
Comparison 1. Current OST versus no OST

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence adjusted analyses by region	12	6361	Risk Ratio (Random, 95% CI)	0.50 [0.40, 0.63]
1.1 North America	5	2245	Risk Ratio (Random, 95% CI)	0.57 [0.42, 0.76]
1.2 Europe	5	3494	Risk Ratio (Random, 95% CI)	0.43 [0.27, 0.68]
1.3 Australia	2	622	Risk Ratio (Random, 95% CI)	0.42 [0.25, 0.72]
2 HCV incidence adjusted analysis by study design	12	6361	Risk Ratio (Random, 95% CI)	0.50 [0.40, 0.63]
2.1 Prospective cohort	10	3467	Risk Ratio (Random, 95% CI)	0.51 [0.40, 0.65]
2.2 Cross-sectional surveys	2	2894	Risk Ratio (Random, 95% CI)	0.46 [0.23, 0.89]
3 HCV incidence unadjusted analyses by different modes of OST provision	9		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Ever used OST	3	375	Risk Ratio (Random, 95% CI)	0.81 [0.52, 1.27]
3.2 Interrupted OST use	3	1157	Risk Ratio (Random, 95% CI)	0.80 [0.57, 1.10]
3.3 Detoxification	1	552	Risk Ratio (Random, 95% CI)	1.45 [0.79, 2.66]
3.4 High dose	2	453	Risk Ratio (Random, 95% CI)	0.52 [0.29, 0.94]

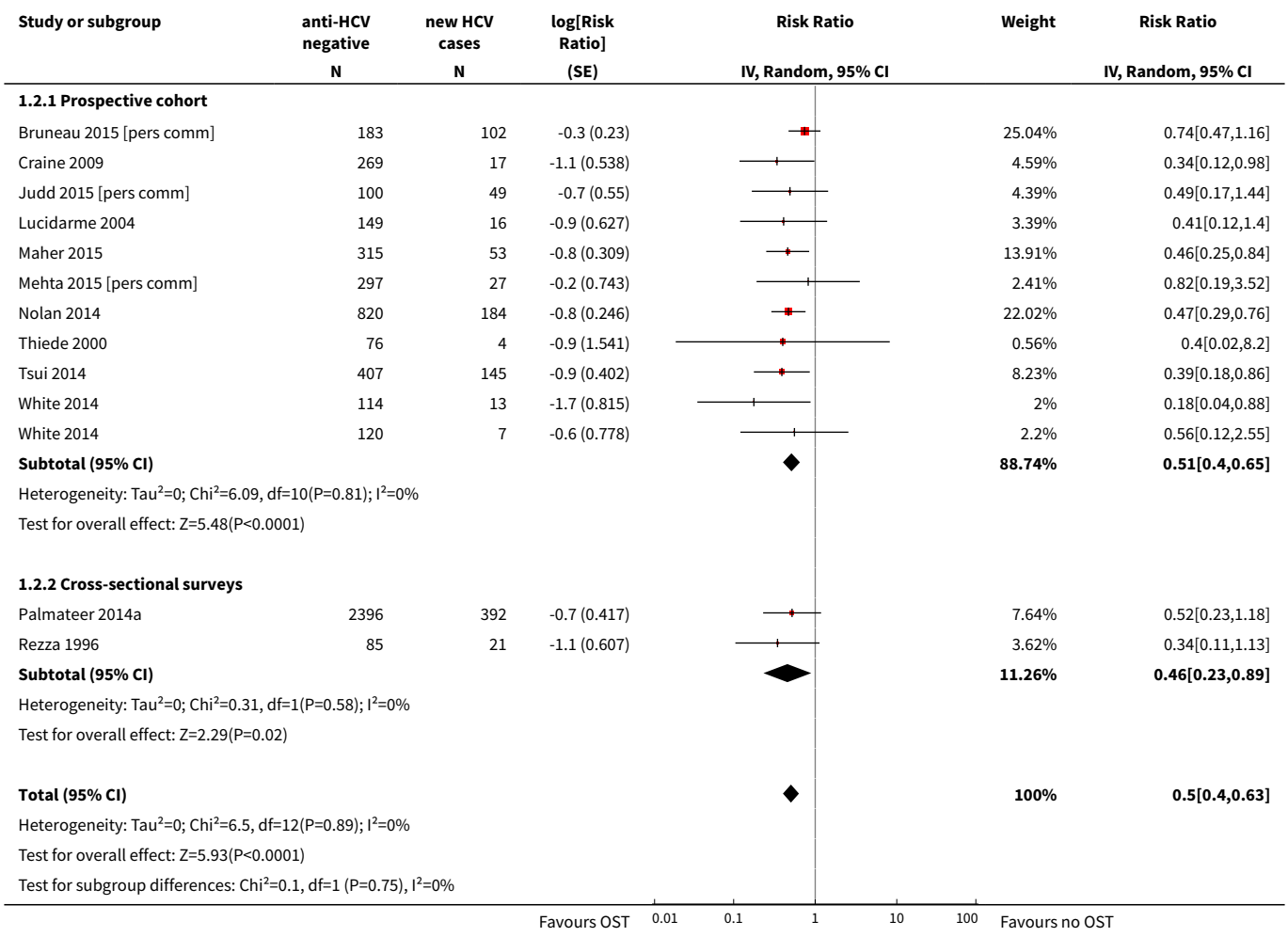
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Low dose	2	453	Risk Ratio (Random, 95% CI)	0.85 [0.44, 1.65]

Analysis 1.1. Comparison 1 Current OST versus no OST, Outcome 1 HCV incidence adjusted analyses by region.

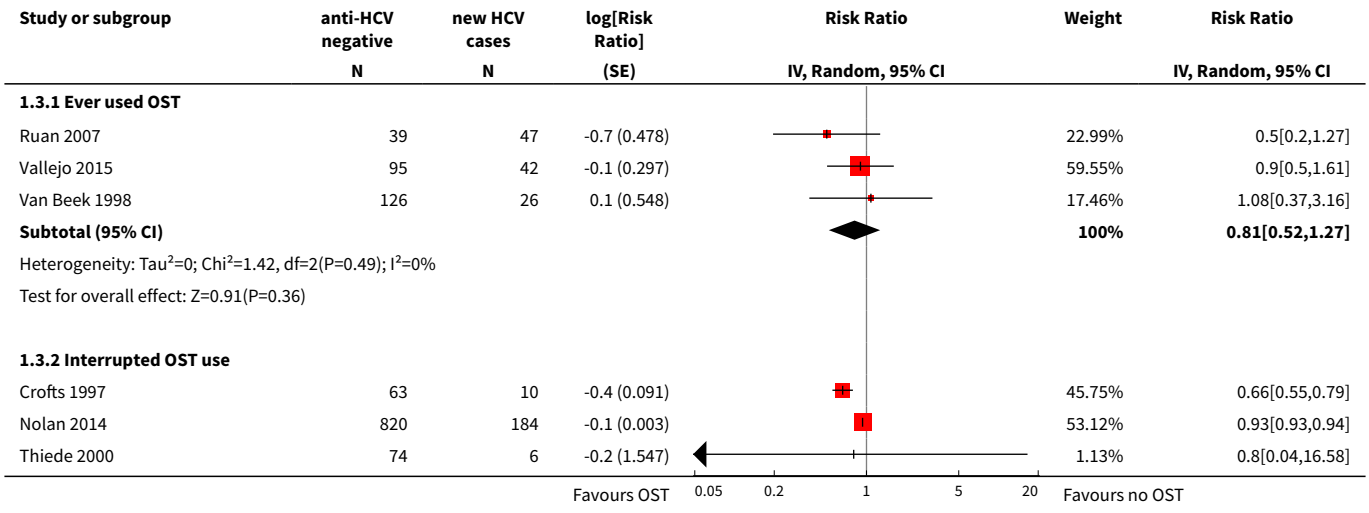
Study or subgroup	anti HCV negative N	HCV new cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 North America						
Bruneau 2015 [pers comm]	183	102	-0.3 (0.23)		25.04%	0.74[0.47,1.16]
Mehta 2015 [pers comm]	297	27	-0.2 (0.743)		2.41%	0.82[0.19,3.52]
Nolan 2014	820	184	-0.8 (0.246)		22.02%	0.47[0.29,0.76]
Thiede 2000	76	4	-0.9 (1.541)		0.56%	0.4[0.02,8.2]
Tsui 2014	407	145	-0.9 (0.402)		8.23%	0.39[0.18,0.86]
Subtotal (95% CI)					**58.26%**	**0.57[0.42,0.76]**
Heterogeneity: Tau^2=0; Chi^2=3.08, df=4(P=0.54); I^2=0%						
Test for overall effect: Z=3.74(P=0)						
1.1.2 Europe						
Craine 2009	269	17	-1.1 (0.538)		4.59%	0.34[0.12,0.98]
Judd 2015 [pers comm]	100	49	-0.7 (0.55)		4.39%	0.49[0.17,1.44]
Lucidarme 2004	149	16	-0.9 (0.627)		3.39%	0.41[0.12,1.4]
Palmateer 2014a	2396	392	-0.7 (0.417)		7.64%	0.52[0.23,1.18]
Rezza 1996	85	21	-1.1 (0.607)		3.62%	0.34[0.11,1.13]
Subtotal (95% CI)					**23.63%**	**0.43[0.27,0.68]**
Heterogeneity: Tau^2=0; Chi^2=0.59, df=4(P=0.96); I^2=0%						
Test for overall effect: Z=3.56(P=0)						
1.1.3 Australia						
Maher 2015	315	53	-0.8 (0.309)		13.91%	0.46[0.25,0.84]
White 2014	120	7	-0.6 (0.778)		2.2%	0.56[0.12,2.55]
White 2014	114	13	-1.7 (0.815)		2%	0.18[0.04,0.88]
Subtotal (95% CI)					**18.11%**	**0.42[0.25,0.72]**
Heterogeneity: Tau^2=0; Chi^2=1.33, df=2(P=0.51); I^2=0%						
Test for overall effect: Z=3.17(P=0)						
Total (95% CI)					**100%**	**0.5[0.4,0.63]**
Heterogeneity: Tau^2=0; Chi^2=6.5, df=12(P=0.89); I^2=0%						
Test for overall effect: Z=5.93(P<0.0001)						
Test for subgroup differences: Chi^2=1.5, df=1 (P=0.47), I^2=0%						

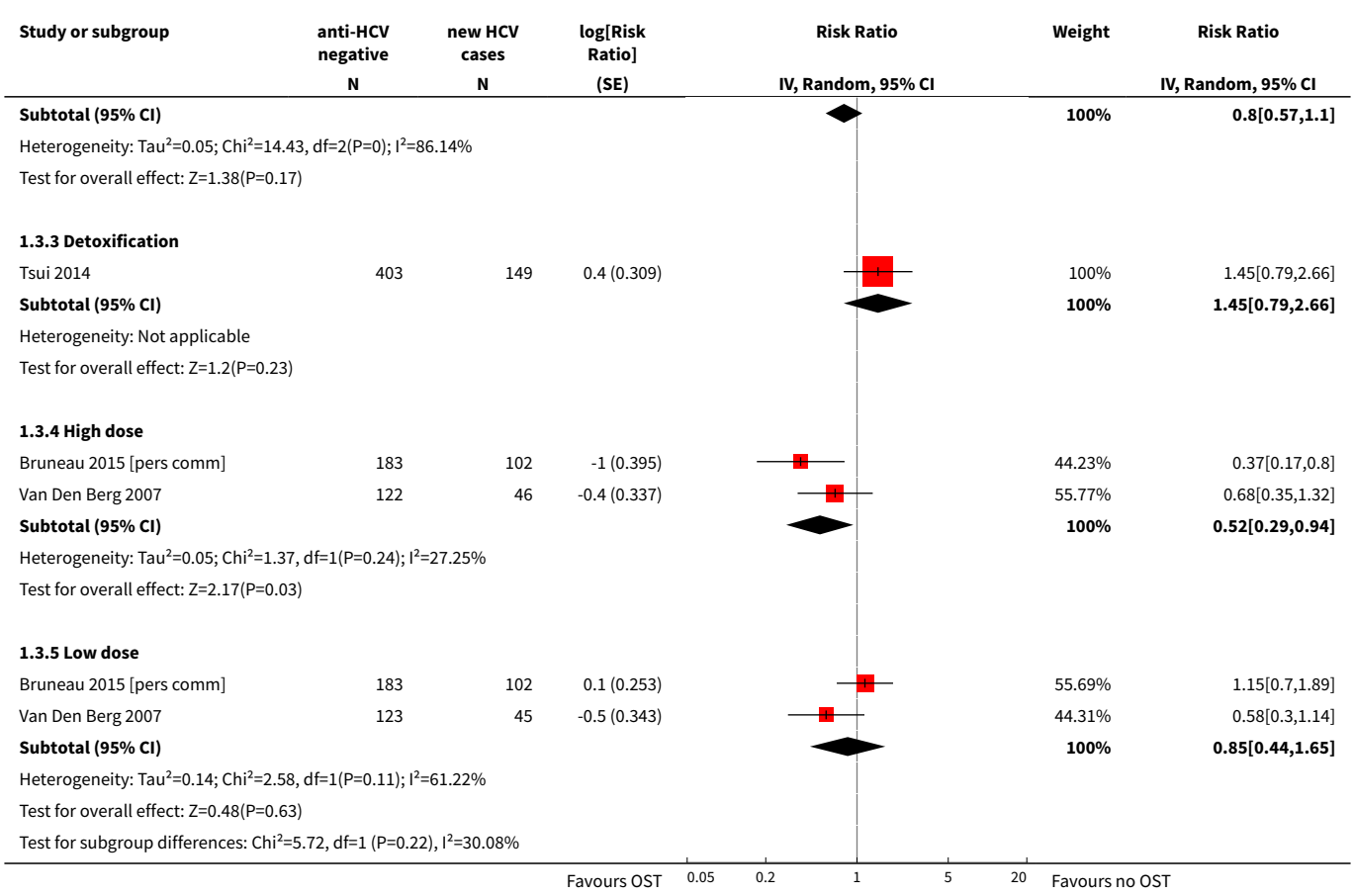


Analysis 1.2. Comparison 1 Current OST versus no OST, Outcome 2 HCV incidence adjusted analysis by study design.



Analysis 1.3. Comparison 1 Current OST versus no OST, Outcome 3 HCV incidence unadjusted analyses by different modes of OST provision.

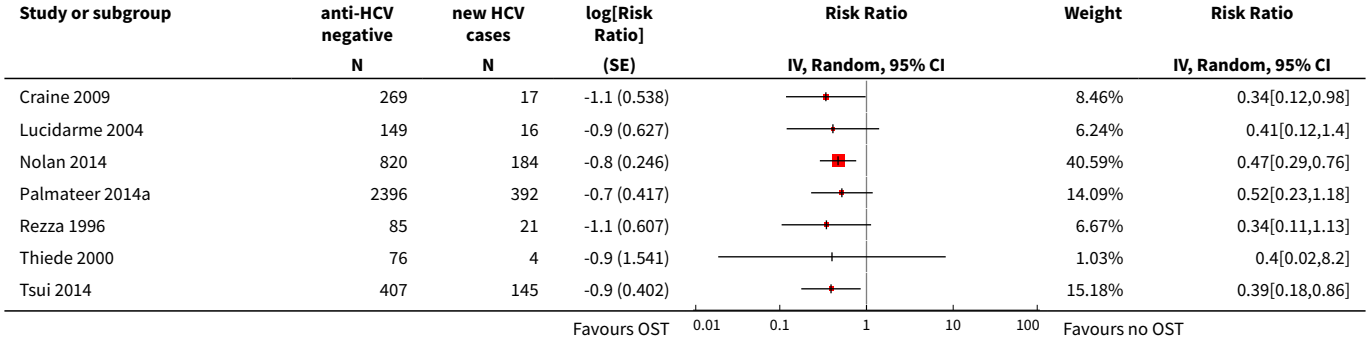


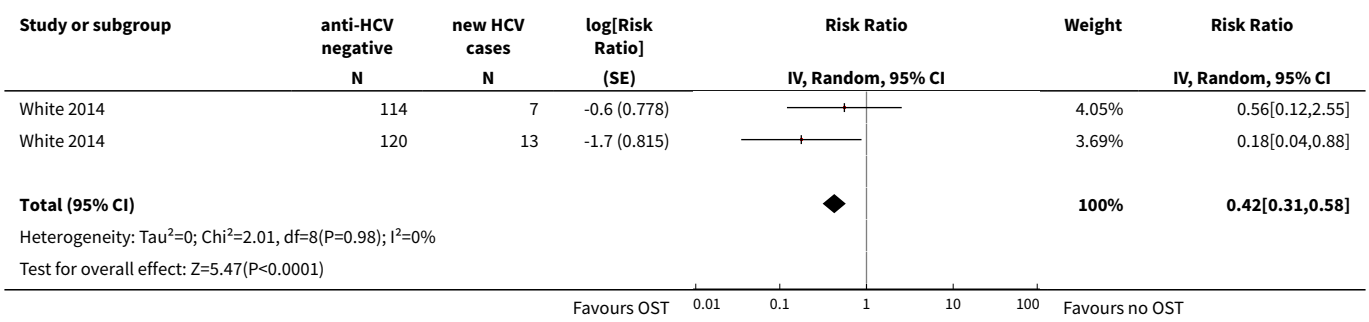


Comparison 2. Sensitivity analysis: OST versus no OST, adjusted analyses excluding unpublished datasets

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	8	5235	Risk Ratio (Random, 95% CI)	0.42 [0.31, 0.58]

Analysis 2.1. Comparison 2 Sensitivity analysis: OST versus no OST, adjusted analyses excluding unpublished datasets, Outcome 1 HCV incidence.

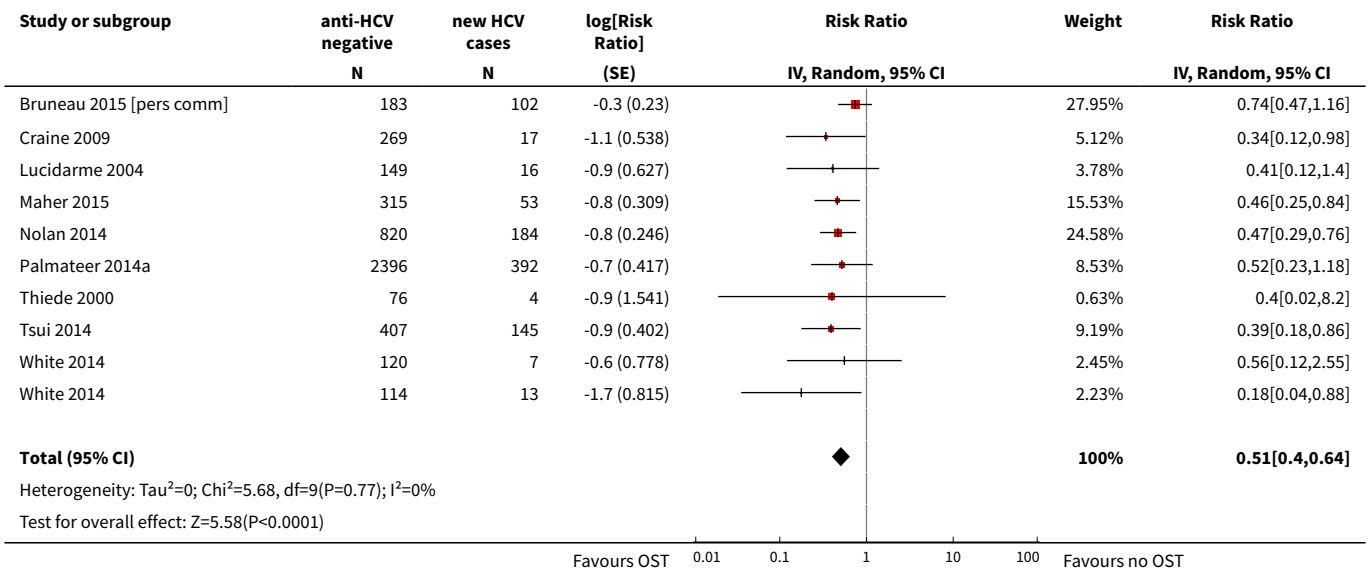




Comparison 3. Sensitivity analysis: OST versus no OST, adjusted analyses excluding studies at critical risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	9	5782	Risk Ratio (Random, 95% CI)	0.51 [0.40, 0.64]

Analysis 3.1. Comparison 3 Sensitivity analysis: OST versus no OST, adjusted analyses excluding studies at critical risk of bias, Outcome 1 HCV incidence.

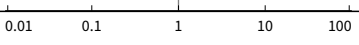


Comparison 4. Sensitivity analysis: OST versus no OST, adjusted analyses excluding cross-sectional studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	10	3467	Risk Ratio (Random, 95% CI)	0.51 [0.40, 0.65]

Analysis 4.1. Comparison 4 Sensitivity analysis: OST versus no OST, adjusted analyses excluding cross-sectional studies, Outcome 1 HCV incidence.

Study or subgroup	anti-HCV negative N	new HCV cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bruneau 2015 [pers comm]	183	102	-0.3 (0.23)		28.22%	0.74[0.47,1.16]
Craine 2009	269	17	-1.1 (0.538)		5.17%	0.34[0.12,0.98]
Judd 2015 [pers comm]	100	49	-0.7 (0.55)		4.95%	0.49[0.17,1.44]
Lucidarme 2004	149	16	-0.9 (0.627)		3.82%	0.41[0.12,1.4]
Maher 2015	315	53	-0.8 (0.309)		15.68%	0.46[0.25,0.84]
Mehta 2015 [pers comm]	297	27	-0.2 (0.743)		2.71%	0.82[0.19,3.52]
Nolan 2014	820	184	-0.8 (0.246)		24.81%	0.47[0.29,0.76]
Thiede 2000	76	4	-0.9 (1.541)		0.63%	0.4[0.02,8.2]
Tsui 2014	407	145	-0.9 (0.402)		9.28%	0.39[0.18,0.86]
White 2014	114	7	-0.6 (0.778)		2.47%	0.56[0.12,2.55]
White 2014	120	13	-1.7 (0.815)		2.26%	0.18[0.04,0.88]
Total (95% CI)					**100%**	**0.51[0.4,0.65]**
Heterogeneity: Tau²=0; Chi²=6.09, df=10(P=0.81); I²=0%						
Test for overall effect: Z=5.48(P<0.0001)						

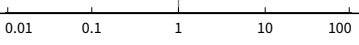


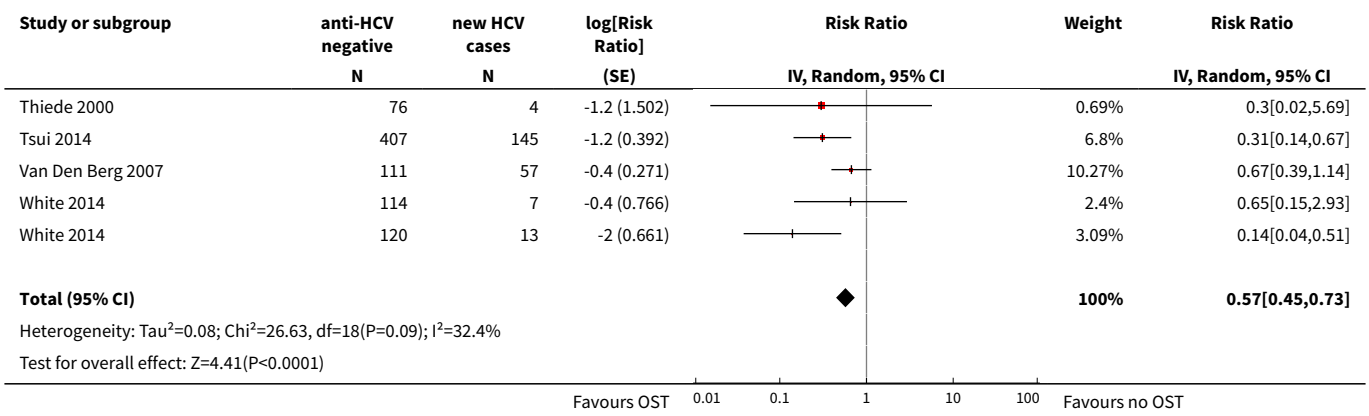
Comparison 5. OST versus no OST, unadjusted analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	16	9499	Risk Ratio (Random, 95% CI)	0.57 [0.45, 0.73]

Analysis 5.1. Comparison 5 OST versus no OST, unadjusted analysis, Outcome 1 HCV incidence.

Study or subgroup	anti-HCV negative N	new HCV cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Aitken 2015 [pers comm]	81	17	-0.2 (0.484)		5.07%	0.8[0.31,2.07]
Bruneau 2015 [pers comm]	183	102	-0.3 (0.23)		11.82%	0.74[0.47,1.16]
Craine 2009	269	17	-1.3 (0.534)		4.37%	0.27[0.09,0.77]
Crofts 1997	60	13	0.6 (0.652)		3.16%	1.8[0.5,6.46]
Hope 2015 [pers comm]	916	3	-1.4 (0.802)		2.21%	0.24[0.05,1.16]
Hope 2015 [pers comm]	917	2	0.3 (1.427)		0.76%	1.31[0.08,21.48]
Hope 2015 [pers comm]	917	2	0.4 (1.23)		1.01%	1.55[0.14,17.27]
Judd 2015 [pers comm]	100	49	-0.8 (0.54)		4.29%	0.47[0.16,1.36]
Lucidarme 2004	149	16	-1.1 (0.561)		4.05%	0.34[0.11,1.02]
Maher 2015	315	53	-0.8 (0.291)		9.6%	0.43[0.24,0.76]
Mehta 2015 [pers comm]	297	27	-0.5 (0.736)		2.57%	0.6[0.14,2.54]
Nolan 2014	820	184	-0.4 (0.201)		13.03%	0.67[0.45,0.99]
Palmateer 2014a	2396	392	-0.7 (0.289)		9.66%	0.51[0.29,0.9]
Spittal 2012	103	45	0.7 (0.476)		5.19%	2.11[0.83,5.37]

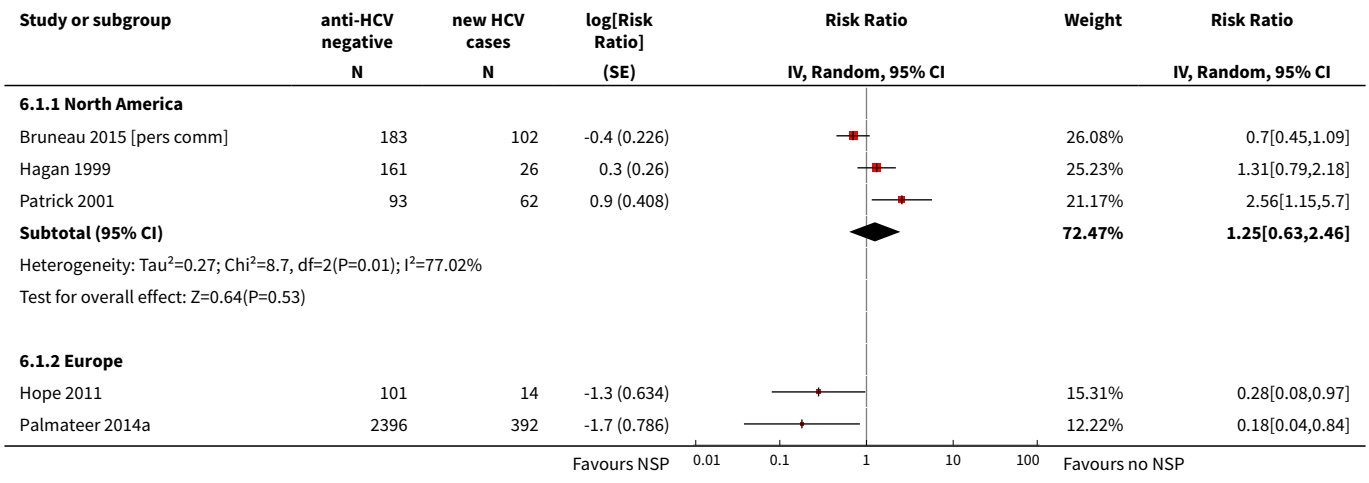


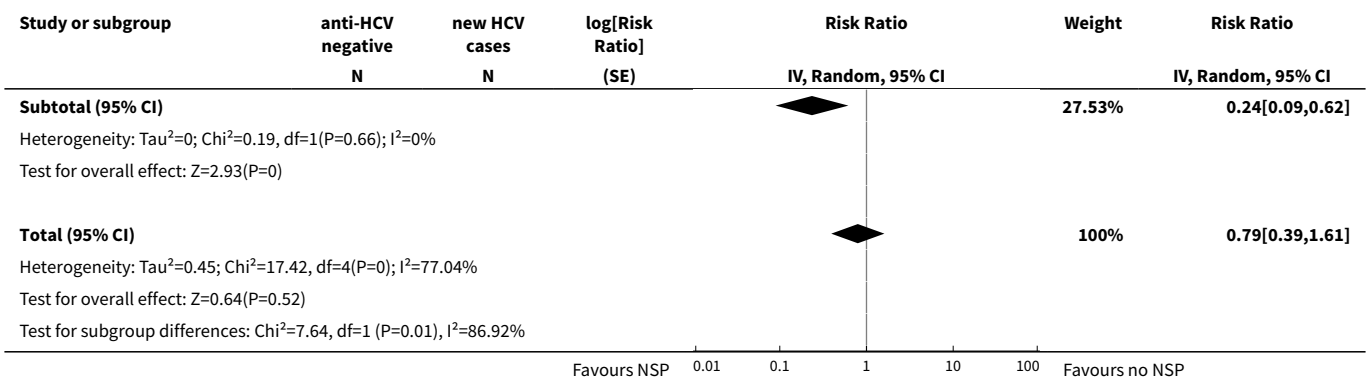


Comparison 6. High NSP coverage versus no/low NSP coverage

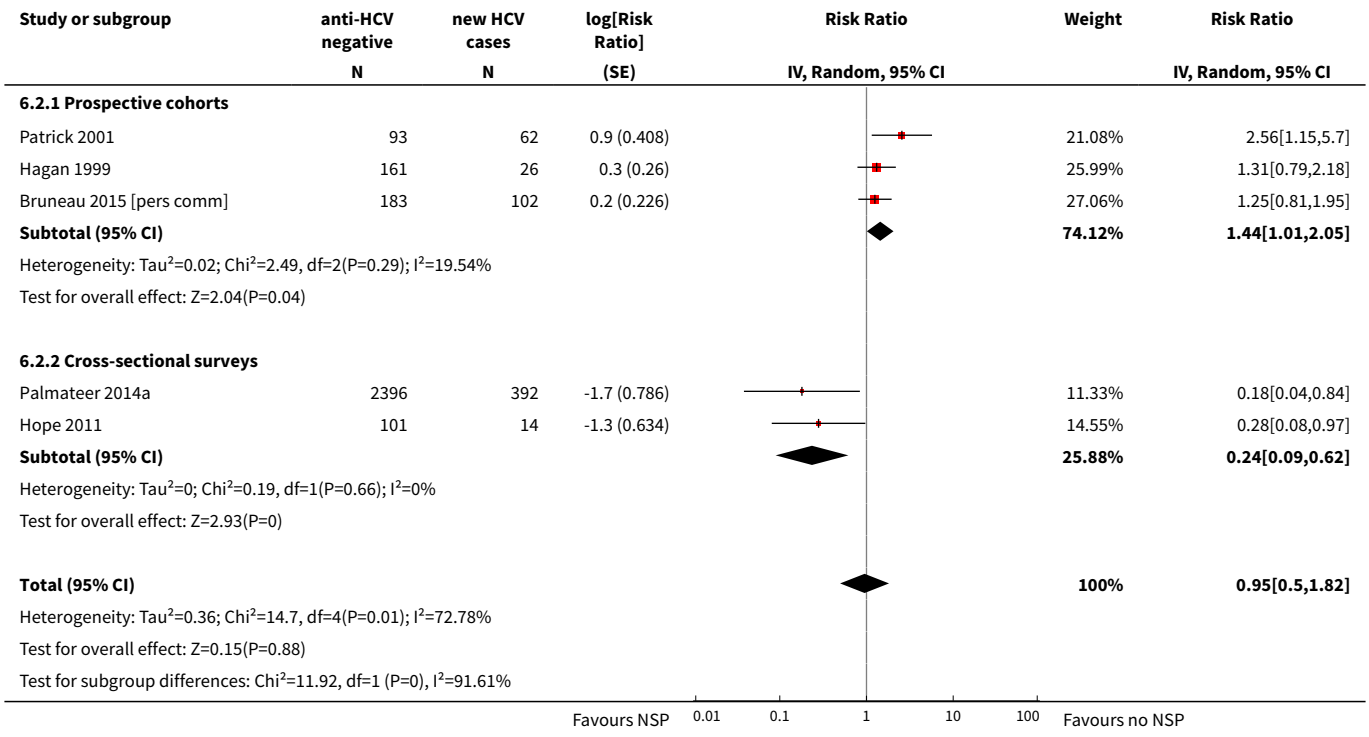
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence adjusted analyses by region	5	3530	Risk Ratio (Random, 95% CI)	0.79 [0.39, 1.61]
1.1 North America	3	627	Risk Ratio (Random, 95% CI)	1.25 [0.63, 2.46]
1.2 Europe	2	2903	Risk Ratio (Random, 95% CI)	0.24 [0.09, 0.62]
2 HCV incidence adjusted analyses by study design	5	3530	Risk Ratio (Random, 95% CI)	0.95 [0.50, 1.82]
2.1 Prospective cohorts	3	627	Risk Ratio (Random, 95% CI)	1.44 [1.01, 2.05]
2.2 Cross-sectional surveys	2	2903	Risk Ratio (Random, 95% CI)	0.24 [0.09, 0.62]

Analysis 6.1. Comparison 6 High NSP coverage versus no/low NSP coverage, Outcome 1 HCV incidence adjusted analyses by region.





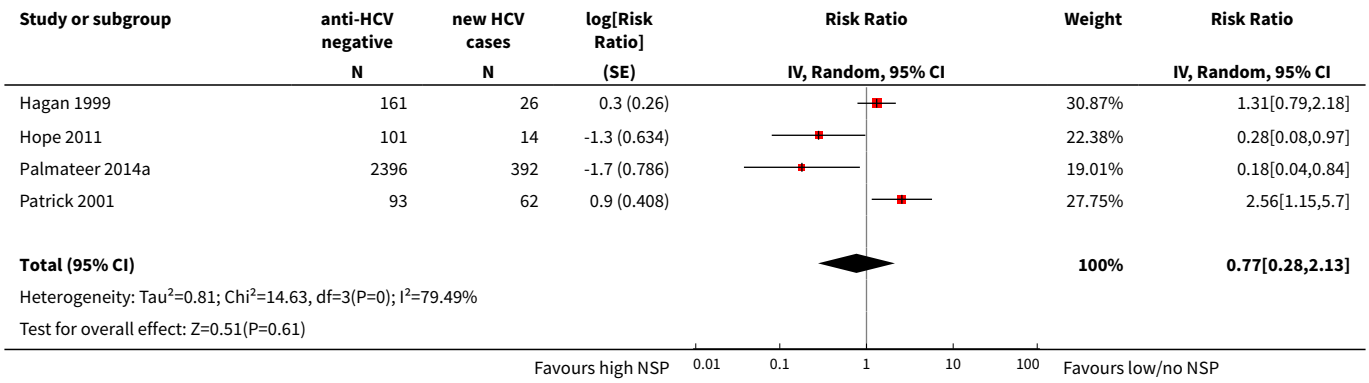
Analysis 6.2. Comparison 6 High NSP coverage versus no/low NSP coverage, Outcome 2 HCV incidence adjusted analyses by study design.



Comparison 7. Sensitivity analysis: high NSP versus low/no NSP, excluding unpublished data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	4	3245	Risk Ratio (Random, 95% CI)	0.77 [0.28, 2.13]

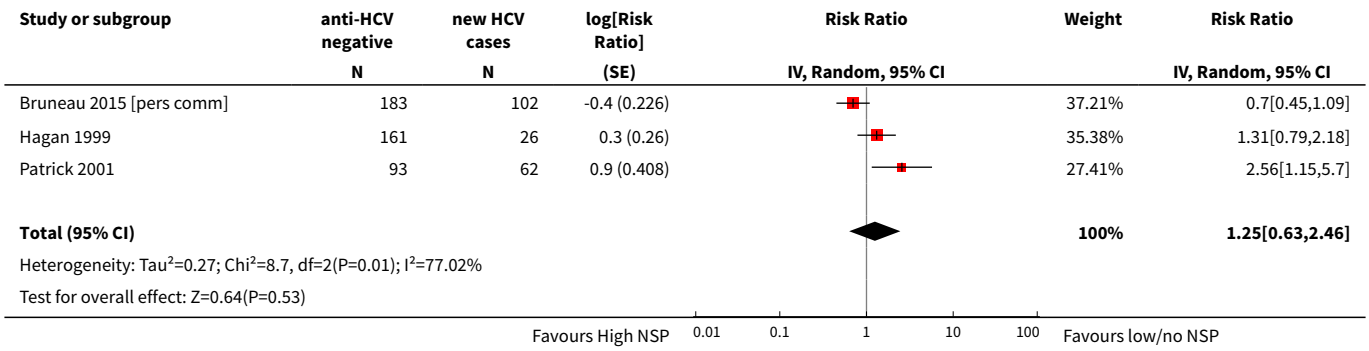
Analysis 7.1. Comparison 7 Sensitivity analysis: high NSP versus low/no NSP, excluding unpublished data, Outcome 1 HCV incidence.



Comparison 8. Sensitivity analysis: high NSP versus low/no NSP, excluding cross-sectional surveys

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	3	627	Risk Ratio (Random, 95% CI)	1.25 [0.63, 2.46]

Analysis 8.1. Comparison 8 Sensitivity analysis: high NSP versus low/no NSP, excluding cross-sectional surveys, Outcome 1 HCV incidence.

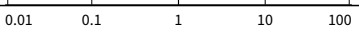


Comparison 9. High NSP coverage versus low/no coverage, unadjusted estimates

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	7	6455	Risk Ratio (Random, 95% CI)	0.78 [0.39, 1.55]

Analysis 9.1. Comparison 9 High NSP coverage versus low/ no coverage, unadjusted estimates, Outcome 1 HCV incidence.

Study or subgroup	anti-HCV negative N	new HCV cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bruneau 2015 [pers comm]	183	102	-0.2 (0.221)		16.16%	0.81[0.52,1.24]
Hagan 1999	161	26	0.4 (0.405)		14.06%	1.42[0.64,3.14]
Hope 2011	101	14	-2.2 (0.79)		9.24%	0.11[0.02,0.54]
Hope 2015 [pers comm]	917	3	-0 (0.787)		9.28%	0.99[0.21,4.63]
Hope 2015 [pers comm]	917	2	-0.3 (1.455)		4.38%	0.73[0.04,12.63]
Hope 2015 [pers comm]	916	2	-0.6 (1.232)		5.55%	0.55[0.05,6.15]
Palmateer 2014a	2396	392	-1.3 (0.612)		11.35%	0.26[0.08,0.86]
Patrick 2001	93	62	1.3 (0.283)		15.53%	3.69[2.12,6.43]
Van Den Berg 2007	138	30	-0.5 (0.374)		14.45%	0.62[0.3,1.29]
Total (95% CI)					**100%**	**0.78[0.39,1.55]**
Heterogeneity: Tau^2=0.72; Chi^2=37.14, df=8(P<0.0001); I^2=78.46%						
Test for overall effect: Z=0.72(P=0.47)						



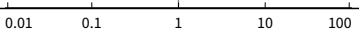
Favours high NSP — Favours low/no NSP

Comparison 10. Low NSP coverage versus no coverage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence, adjusted analyses	6	2765	Risk Ratio (Random, 95% CI)	1.43 [0.82, 2.49]

Analysis 10.1. Comparison 10 Low NSP coverage versus no coverage, Outcome 1 HCV incidence, adjusted analyses.

Study or subgroup	anti-HCV negative N	new HCV cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Hagan 1995	26	20	-2 (0.767)		9.29%	0.14[0.03,0.62]
Hagan 1999	171	16	1 (0.606)		12.5%	2.59[0.79,8.5]
Holtzman 2009	1149	139	0.4 (0.222)		24.88%	1.49[0.96,2.3]
Maher 2015	315	53	0.4 (0.293)		22.32%	1.56[0.88,2.77]
Mehta 2015 [pers comm]	316	8	-0.3 (1.03)		5.99%	0.76[0.1,5.73]
Page 2015 [pers comm]	381	171	1 (0.218)		25.01%	2.62[1.71,4.02]
Total (95% CI)					**100%**	**1.43[0.82,2.49]**
Heterogeneity: Tau^2=0.27; Chi^2=16.2, df=5(P=0.01); I^2=69.13%						
Test for overall effect: Z=1.26(P=0.21)						



Favours Low NSP coverage — Favours no coverage

Comparison 11. Low NSP coverage versus no NSP, unadjusted analysis

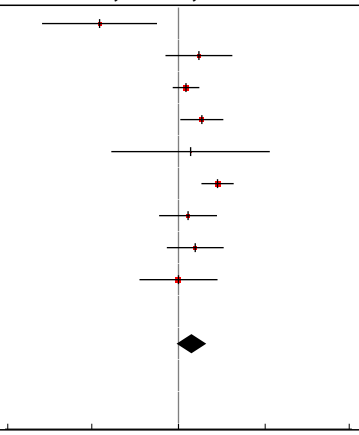
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence	9	3242	Risk Ratio (Random, 95% CI)	1.41 [0.95, 2.09]

Analysis 11.1. Comparison 11 Low NSP coverage versus no NSP, unadjusted analysis, Outcome 1 HCV incidence.

Study or subgroup	anti-HCV negative N	HCV new cases N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Hagan 1995	26	20	-2.1 (0.779)		5.06%	0.12[0.03,0.57]
Hagan 1999	171	16	0.5 (0.453)		10.19%	1.72[0.71,4.18]
Holtzman 2009	1149	139	0.2 (0.18)		18.05%	1.22[0.86,1.74]
Maher 2015	315	53	0.6 (0.291)		14.64%	1.86[1.05,3.29]
Mehta 2015 [pers comm]	316	8	0.3 (1.075)		3%	1.38[0.17,11.35]
Page 2015 [pers comm]	381	0	1 (0.219)		16.88%	2.82[1.84,4.33]
Thorpe 2002	324	29	0.3 (0.392)		11.7%	1.29[0.6,2.78]
Van Den Berg 2007	139	29	0.4 (0.385)		11.9%	1.56[0.73,3.32]
White 2014	102	25	0 (0.529)		8.58%	1[0.35,2.82]
Total (95% CI)					**100%**	**1.41[0.95,2.09]**

Heterogeneity: Tau^2=0.19; Chi^2=21.21, df=8(P=0.01); I^2=62.28%

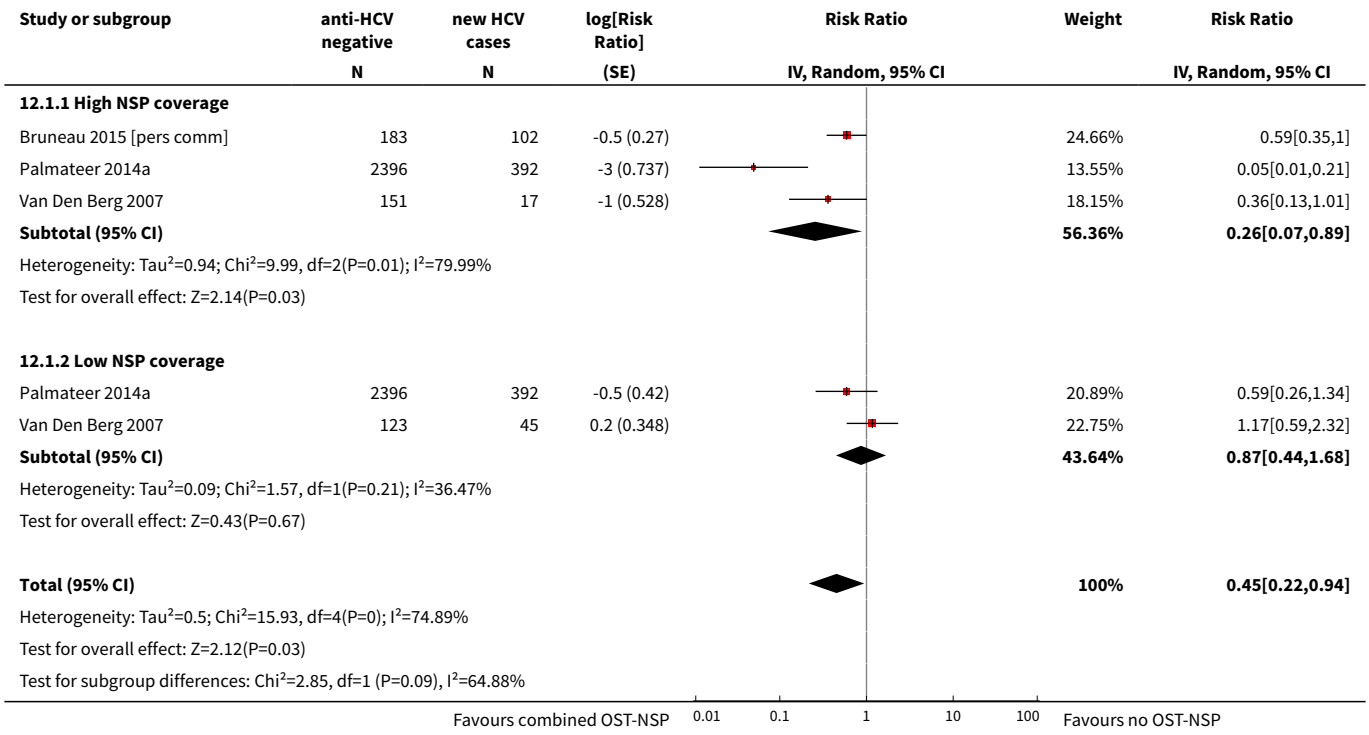
Test for overall effect: Z=1.71(P=0.09)



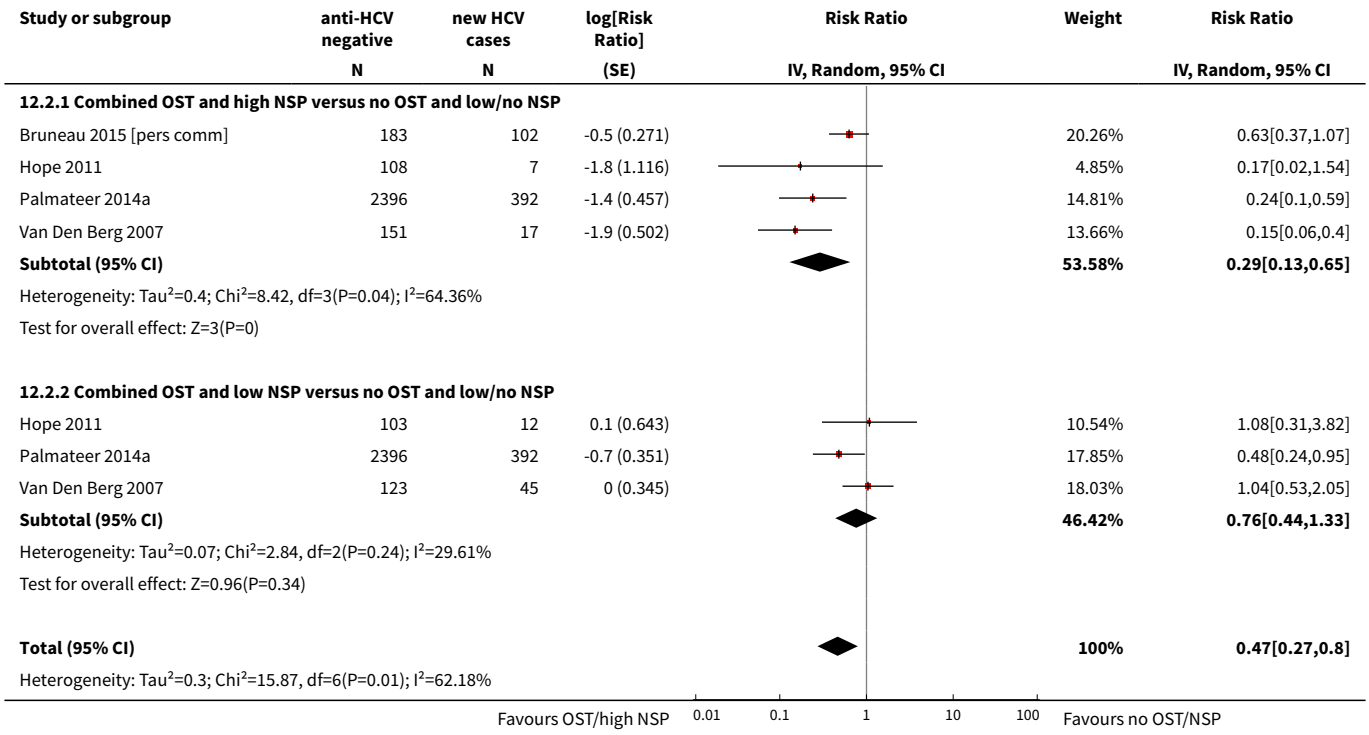
Comparison 12. Combined OST and high/low NSP versus no OST and low/no NSP

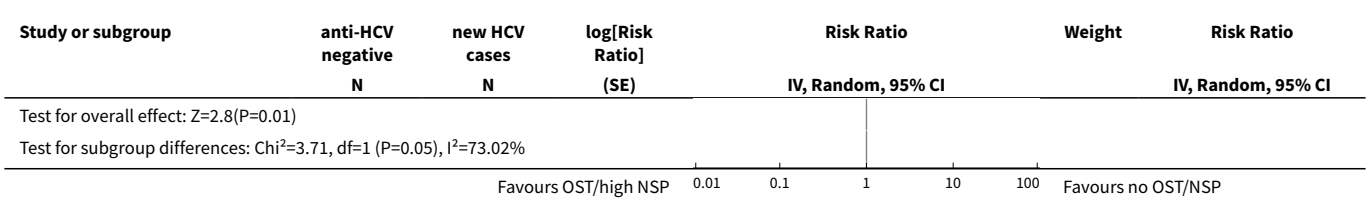
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HCV incidence adjusted analyses	3	6197	Risk Ratio (Random, 95% CI)	0.45 [0.22, 0.94]
1.1 High NSP coverage	3	3241	Risk Ratio (Random, 95% CI)	0.26 [0.07, 0.89]
1.2 Low NSP coverage	2	2956	Risk Ratio (Random, 95% CI)	0.87 [0.44, 1.68]
2 HCV incidence unadjusted analyses	4	6427	Risk Ratio (Random, 95% CI)	0.47 [0.27, 0.80]
2.1 Combined OST and high NSP versus no OST and low/no NSP	4	3356	Risk Ratio (Random, 95% CI)	0.29 [0.13, 0.65]
2.2 Combined OST and low NSP versus no OST and low/no NSP	3	3071	Risk Ratio (Random, 95% CI)	0.76 [0.44, 1.33]

Analysis 12.1. Comparison 12 Combined OST and high/low NSP versus no OST and low/no NSP, Outcome 1 HCV incidence adjusted analyses.



Analysis 12.2. Comparison 12 Combined OST and high/low NSP versus no OST and low/no NSP, Outcome 2 HCV incidence unadjusted analyses.





ADDITIONAL TABLES

Table 1. Risk of bias of included studies

Study	Confounding	Selection bias	Measurement of interventions	Departures from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall risk of bias
Aitken 2015 [pers comm]	Critical	Critical	Serious	No info	Critical	Low	No info	Critical
Bruneau 2015 [pers comm]	Moderate	Serious	Moderate	No info	No info	Low	Low	Serious
Craine 2009	Serious	Serious	Serious	No info	Serious	Low	Low	Serious
Crofts 1997	Critical	Serious	Low	No info	Serious	Serious	Low	Critical
Hagan 1995	Serious	Serious	Serious	No info	Low	Low	Low	Serious
Hagan 1999	Moderate	Serious	Low	No info	Low	Low	Low	Serious
Holtzman 2009	Serious	Serious	Moderate	No info	No info	Low	Low	Serious
Hope 2011	Moderate	Moderate	Serious	No info	Low	Low	Low	Serious
Hope 2015 [pers comm]	Moderate	Moderate	Serious	No info	No info	Low	Low	Serious
Judd 2015 [pers comm]	Moderate	Critical	Critical	No info	Critical	Low	Low	Critical
Lucidarme 2004	Moderate	Serious	Serious	No info	Serious	Low	Low	Serious
Maher 2015	Moderate	Serious	Serious	No info	No info	Low	Low	Serious
Mehta 2015 [pers comm]	Moderate	No info	No info	No info	No info	Low	Low	No info
Nolan 2014	Serious	Serious	Moderate	No info	Low	Low	Low	Serious
Page 2015 [pers comm]	Moderate	No info	No info	No info	No info	Low	Low	No info
Palmateer 2014a	Serious	Serious	Moderate	No info	Serious	Low	Low	Serious
Patrick 2001	Serious	Moderate	Serious	No info	Serious	Low	Low	Serious
Rezza 1996	Serious	Low	Serious	No info	Critical	Low	Low	Critical
Roy 2007	Serious	Serious	Serious	No info	Critical	Low	Low	Critical

Table 1. Risk of bias of included studies *(Continued)*

Ruan 2007	Critical	Critical	Serious	No info	Serious	Low	Low	Critical
Spittal 2012	Serious	Serious	Moderate	No info	Low	Low	Low	Serious
Thiede 2000	Moderate	Moderate	Low	No info	Low	Low	Low	Moderate
Thorpe 2002	Serious	Serious	Serious	No info	Moderate	Low	Low	Serious
Tsui 2014	Moderate	Moderate	Low	No info	Moderate	Low	Low	Moderate
Vallejo 2015	Serious	Serious	Low	No info	Serious	Low	Low	Serious
Van Beek 1998	Critical	Serious	Serious	No info	Critical	Low	Low	Critical
Van Den Berg 2007	Serious	Serious	Moderate	No info	Serious	Low	Low	Serious
White 2014	Moderate	Serious	Moderate	No info	No info	Low	Low	Serious

Table 2. Univariable meta-regression analysis for studies measuring impact of current use of OST on HCV incidence

Variable	Studies	Univariable rate ratio (95% CI)	Ratio of rate ratios (95% CI)	P value	Tau^2
Geographic region					
Europe	8	0.51 (0.37-0.70)	1.0 (ref)	—	—
Australia	5	0.55 (0.28-1.11)	1.12 (0.52-2.41)	—	—
North America	6	0.69 (0.44-1.08)	1.42 (0.73-2.78)	0.53	0.10
Site of recruitment					
Service attenders	12	0.67 (0.49-0.92)	1.0 (ref)	—	—
Community	7	0.49 (0.33-0.73)	0.73 (0.42-1.27)	0.256	0.06
Study design					
Cross-sectional	4	0.51 (0.31-0.85)	1.0	—	—
Prospective cohort	15	0.58 (0.43-0.77)	1.12 (0.48-2.61)	0.784	0.10
Females	17	—	**1.59 (1.13-2.29)**	0.01	0.04
Prison experience	11	—	1.057 (0.61-1.79)	0.821	0.43
Experience of homelessness	12	—	1.08 (0.83-1.40)	0.521	0.23
Injection of stimulants	12	—	0.89 (0.65-1.22)	0.373	0.17
Daily injection	7	—	0.88 (0.64-1.22)	0.373	0.17

CI: confidence interval; **HCV**: hepatitis C virus; **OST**: opioid substitution therapy.

Table 3. Univariable meta-regression analysis for studies measuring impact of high NSP coverage on HCV incidence

Variable	Studies	Univariable rate ratio (95%CI)	Ratio of rate ratios (95%CI)	P value	Tau^2
Geographic region					
Europe	5	0.44 (0.24-0.80)	1.0 (Ref)	—	—
North America	3	1.58 (0.57-4.42)	**3.73 (0.95-14.7)**	0.057	0.41
Recruitment site					
Service attenders	3	0.67 (0.28-1.59)	1.0 (Ref)	—	—
Community	5	0.82 (0.29-2.32)	0.76(0.12-4.88)	0.74	0.89

Table 3. Univariable meta-regression analysis for studies measuring impact of high NSP coverage on HCV incidence *(Continued)*

Study design					
Cross-sectional survey	3	0.34 (0.16-0.75)	1.0 (Ref)	—	—
Prospective cohort	4	1.26 (0.55-2.93)	3.53 (0.78-15.86)	0.087	0.48
Females	7	—	2.97(0.38-23.1)	0.24	0.87
Prison experience	3	—	NA	—	—
Experience of homelessness	6	—	1.01 (0.38-2.67)	0.976	1.53
Injection of stimulants	7	—	1.08 (0.47-2.51)	0.827	1.15
Daily injection	5	—	3.66 (0.22-61.3)	0.239	1.15

CI: confidence interval; **HCV**: hepatitis C virus; **NSP**: needle syringe programmes.

APPENDICES

Appendix 1. Search strategies to identify studies that measure the impact of NSP/OST on HCV incidence

Cochrane Drug and Alcohol Group Specialised Register (CRS)

1. (HCV) AND (INREGISTER)
2. ("hepatitis C") AND (INREGISTER)
3. ("hep C") AND (INREGISTER)
4. #1 OR #2 OR #3

CENTRAL, DARE, NHSEED and HTA (Cochrane Library)

1. MeSH descriptor: [Needle-Exchange Programs] explode all trees
2. MeSH descriptor: [Community Pharmacy Services] explode all trees
3. ((needle* or syringe* or inject*) near/3 exchange):ti,ab,kw (Word variations have been searched)
4. MeSH descriptor: [Harm Reduction] explode all trees
5. (harm near/2 reduc*):ti,ab,kw (Word variations have been searched)
6. (needle* or syringe* or inject*) near/3 (suppl* or access* or provision or provid* or distribut* or dispens* or pack*):ti,ab,kw (Word variations have been searched)
7. (needle* or syringe* or inject*) near/3 (program* or service* or center* or centre* or scheme* or facility or facilities or area* or pharmacy or pharmacies or unit or units or room*):ti,ab,kw (Word variations have been searched)
8. (needle* or syringe* or inject* or slot or dispensing or vending) near/3 (machine* or (peer next distrib*)):ti,ab,kw (Word variations have been searched)
9. #1 or #2 or #3 or #4 or #5 or #5 or #6 or #7 or #8
10. MeSH descriptor: [Substance Abuse, Intravenous] explode all trees
11. ((substance* or drug* or opiate* or opioid* or heroin* or morphin* or morfin* or narcot*) near/6 (use* or abus* or misuse* or addict* or depend*)):ti,ab,kw (Word variations have been searched)
12. (substance* or drug) and (inject* or intravenous):ti,ab,kw (Word variations have been searched)
13. #10 or #11 or #12
14. MeSH descriptor: [Opiate Substitution Treatment] explode all trees
15. MeSH descriptor: [Methadone] explode all trees
16. MeSH descriptor: [Buprenorphine] explode all trees
17. (substitut* or maint*) near/2 (treatment or therapy):ti,ab,kw (Word variations have been searched)
18. (methadone or buprenorphine or subutex or suboxone):ti,ab,kw (Word variations have been searched)

19.#13 or #14 or #15 or #16 or #17 or #18
20.#9 or #19
21.MeSH descriptor: [Hepatitis C] explode all trees
22.(hepatitis next C) or (hep next C):ti,ab,kw (Word variations have been searched)
23.HCV:ti,ab
24.#21 or #22 or #23
25.#13 and #20 and #24

MEDLINE, PsycINFO and Global Health (Ovid)

1. Needle-Exchange Programs/
2. Community pharmacy services/
3. ((needle* or syringe* or inject*) adj3 exchange).ab,ti.
4. Harm Reduction/
5. (harm adj reduc*).ab,ti.
6. ((needle* or syringe* or inject*) adj3 (suppl* or access* or provision or provid* or distribut* or dispens* or pack*)).ab,ti.
7. ((needle* or syringe* or inject*) adj3 (program* or service* or center* or centre* or scheme* or facility or facilities or area* or pharmacy or pharmacies or unit or units or room*)).ab,ti.
8. ((needle* or syringe* or inject* or slot or dispensing or vending) adj3 (machine* or (peer adj distrib*))).ab,ti.
9. or/1-8
10. Substance Abuse, Intravenous/
11. (substance$ or drug$).ab,ti.
12. (abuse$ or depend$ or use$ or misus$ or addict$).ab,ti.
13. (inject$ or intravenous).ab,ti.
14. 10 or (11 and 12) or (11 and 13)
15. opiate substitution treatment/
16. methadone/
17. buprenorphine/
18. (((substitut* or maint*) adj2 (treatment or therapy)) or methadone or buprenorphine or subutex or suboxone).ab,ti.
19. or/15-18
20. exp Hepatitis C/
21. (hepatitis-c or or hep c or hcv).ab,ti.
22. 20 or 21
23. (9 or 19) and 14 and 22

EMBASE (embase.com)

'substance abuse'/exp OR 'substance abuse' OR ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) NEAR/6 (use* OR abus* OR misuse* OR addict* OR depend*)):ab,ti OR ((substance* OR drug*) NEAR/6 (inject* OR intravenous)):ab,ti AND ('hepatitis c'/exp OR 'hepatitis-c':ab,ti OR 'hep c':ab,ti OR hcv:ab,ti) AND ('preventive health service'/exp OR ((needle* OR syringe* OR inject*) NEAR/3 exchange):ab,ti OR 'harm reduction'/exp OR (harm NEAR/2 reduc*):ab,ti OR ((needle* OR syringe* OR inject*) NEAR/3 (suppl* OR access* OR provision OR provid* OR distribut* OR dispens* OR pack*)):ab,ti OR ((needle* OR syringe* OR inject*) NEAR/3 (program* OR service* OR center* OR centre* OR scheme* OR facility OR facilities OR area* OR pharmacy OR pharmacies OR unit OR units OR room*)):ab,ti OR ((needle* OR syringe* OR inject* OR slot OR dispensing OR vending) NEAR/3 (machine* OR peer)):ab,ti OR 'opiate substitution treatment'/exp OR 'methadone'/exp OR methadone:ab,ti OR 'buprenorphine'/exp OR 'buprenorphine':ab,ti OR ((substitut* OR maint*) NEAR/2 (treatment OR therapy)):ab,ti OR subutex:ab,ti OR suboxone:ab,ti)

CINAHL (EBSCO)

1. (MH "Needle Exchange Programs")
2. TI((needle* OR syringe*OR inject*) N3 exchange) OR AB(needle* OR syringe* OR inject*) N3 exchange)
3. (MH "Harm Reduction")
4. TI (harm N2 reduc*) OR AB (harm N2 reduc*)
5. TI ((needle* OR syringe* OR inject*) N3 (suppl* OR access* OR provision OR provid* OR distribut* OR dispens* OR pack*)) OR AB (TI(needle* OR syringe* OR inject*) N3 (suppl* OR access* OR provision OR provid* OR distribut* OR dispens* OR pack*))

6. TI ((needle* OR syringe* OR inject*) N3 (program* OR service* OR center* OR centre* OR scheme* OR facility OR facilities OR area* OR pharmacy OR pharmacies OR unit OR units OR room*)) OR AB ((needle* OR syringe* OR inject*) N3 (program* OR service* OR center* OR centre* OR scheme* OR facility or facilities OR area* OR pharmacy OR pharmacies OR unit OR units OR room*))
7. TI (((needle* OR syringe* OR inject* OR slot OR dispensing OR vending) N3 (machine*OR (peer N2 distrib*)))) OR AB (((needle* OR syringe* OR inject* OR slot OR dispensing OR vending) N3 (machine* OR (peer N2 distrib*))))
8. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7
9. (MH "Substance Abuse, Intravenous")
10. TI ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) N6 (use* OR abus* OR misuse* OR addict* OR depend*))
11. AB ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) N6 (use* OR abus* OR misuse* OR addict* ORdepend*))
12. TI (substance* OR drug*) AND TI (inject* OR intravenous)
13. AB(substance* OR drug*) AND AB(inject* OR intravenous)
14. S9 OR S10 OR S11 OR S12 OR S13
15. (MH "Methadone") OR (MH "Buprenorphine")
16. TI (methadone or buprenorphine or subutex or suboxone) OR AB (methadone or buprenorphine or subutex or suboxone)
17. TX (substitut* or maint*) N2 (treatment or therapy)
18. S15 OR S16 OR S17
19. (MH "Hepatitis C+")
20. TI ("hepatitis-c" or "hep c" or hcv) OR AB ("hepatitis-c" or "hep c" or hcv)
21. S19 OR S20
22. S8 OR S18
23. S14 AND S21 AND S22

Web of Science (THOMSON REUTERS)

1. TOPIC: (((needle* OR syringe* OR inject*) NEAR/3 exchange))
2. TOPIC: (harm NEAR/2 reduc*)
3. TOPIC: (((needle* OR syringe* OR inject*) NEAR/3 (suppl* OR access* OR provision OR provid* OR distribut* OR dispens* OR pack*)))
4. TOPIC: ((needle* or syringe* or inject*) near/3 (program* or service* or center* or centre* or scheme* or facility or facilities or area* or pharmacy or pharmacies or unit or units or room*))
5. TOPIC: ((needle* or syringe* or inject* or slot or dispensing or vending) NEAR/3 (machine* orpeer))
6. #5 OR #4 OR #3 OR #2 OR #1
7. TOPIC: (((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) NEAR/6 (use* OR abus* OR misuse* OR addict* OR depend*)))
8. TOPIC: ((substance* or drug) and (inject* or intravenous))
9. #8 OR #7
10. TOPIC: ((substitut* or maint*) near/2 (treatment or therapy))
11. TOPIC: ((methadone or buprenorphine or subutex or suboxone))
12. #11 OR #10
13. TOPIC: ("Hepatitis C")
14. TOPIC: ("Hep C")
15. TOPIC: (HCV)
16. #15 OR #14 OR #13
17. #12 OR #6
18. #17 AND #16 AND #9

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

Appendix 2. Search strategies to identify longitudinal studies

MEDLINE, PsycINFO & Global Health (Ovid)

1. Substance Abuse, Intravenous/
2. (substance$ or drug$).ab,ti.
3. (abuse$ or depend$ or use$ or misus$ or addict$).ab,ti.

4. (inject$ or intravenous).ab,ti.
5. 1 or (2 and 3) or (2 and 4)
6. exp Hepatitis C/
7. (hepatitis-c or hcv).ab,ti.
8. (HCV adj2 seroconvers$).ti,ab.
9. (HCV adj2 transmission).ti,ab.
10. or/6-9
11. exp Cohort Studies/
12. exp Longitudinal Studies/
13. (prospective or longitudinal or cohort).ti,ab.
14. or/11-13
15. 5 and 10 and 14
16. Animals/
17. 15 not 16

Embase (embase.com)

'substance abuse'/exp OR ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) NEAR/6 (use* OR abus* OR misuse* OR addict* OR depend*)):ab,ti OR ((substance* OR drug*) NEAR/6 (inject* OR intravenous)):ab,ti AND ('hepatitis c'/exp OR 'hepatitis-c':ab,ti OR 'hep c':ab,ti ORhcv:ab,ti) AND ('cohort analysis'/exp OR 'longitudinal study'/exp OR prospective:ab,ti OR longitudinal:ab,ti OR cohort:ab,ti)

CINAHL (EBSCO)

1. (MH "Substance Abuse, Intravenous")
2. TI ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) N6 (use* OR abus* OR misuse* OR addict* OR depend*))
3. AB ((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) N6 (use* OR abus* OR misuse* OR addict* OR depend*))
4. TI (substance* OR drug*) AND TI (inject* OR intravenous)
5. AB(substance* OR drug*) AND AB(inject* OR intravenous)
6. S1 OR S2 OR S3 OR S4 OR S5
7. (MH "Hepatitis C+")
8. TI ("hepatitis-c" or "hep c" or hcv) OR AB ("hepatitis-c" or "hep c" or hcv)
9. S7 OR S8
10. (MH "Prospective Studies+")
11. TI (prospective or longitudinal or cohort) OR AB (prospective or longitudinal or cohort)
12. S10 OR S11
13. S6 AND S9 AND S12

Web of Science (THOMSON REUTERS)

1. TOPIC: (((substance* OR drug* OR opiate* OR opioid* OR heroin* OR morphin* OR morfin* OR narcot*) NEAR/6 (use* OR abus* OR misuse* OR addict* OR depend*)))
2. TOPIC: ((substance* or drug) and (inject* or intravenous))
3. #1 OR #2
4. TOPIC: ("Hepatitis C")
5. TOPIC: ("Hep C")
6. TOPIC: (HCV)
7. #4 OR #5 OR #6
8. TOPIC: (prospective or longitudinal or cohort)
9. #3 AND #7 AND #8

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

Appendix 3. Criteria for risk of bias assessment for RCTs

Item	Judgment	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgment of the clinician; results of a laboratory test or a series of tests; availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgment of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgment of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment.
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgment of low or high risk
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgment of low or high risk

(Continued)

5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgment of low or high risk
6.Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgment of low or high risk
7. Incomplete outcome data (attrition bias) For all outcomes except retention in treatment or drop out	Low risk	No missing outcome data Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically-relevant impact on the intervention effect estimate For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically-relevant impact on observed effect size Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size

(Continued)

		'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgment of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropout not reported for each group)
8 Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's pre-specified primary outcomes have been reported One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgment of low or high risk

Appendix 4. Criteria for risk of bias assessment for observational studies

Domain	Judgment	Description
Bias due to confounding	**Low risk** (the study is comparable to a well-performed randomised trial with regard to this domain)	No confounding expected
	Moderate risk (the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well performed randomised trial)	Confounding expected, all known critically important confounding domains appropriately measured and adjusted for; and Reliability and validity of measurement of a critically important domains were sufficient that we do not expect serious residual confounding.
	Serious risk (the study has some important problems)	At least one known critically important domain not appropriately measured, or not adjusted for; or

(Continued)

		Reliability or validity of measurement of a critically important domain was low enough that we expect serious residual confounding.
	Critical risk (the study is too problematic to provide any useful evidence on the effects of intervention)	Confounding inherently not controllable, or use of negative controls strongly suggests unmeasured confounding
	No information on which to base a judgment about risk of bias for this domain	No information on whether confounding might be present
Bias in selection of participants into the study	**Low risk**	All participants who would have been eligible for the target trial were included in the study and start of follow-up and start of intervention coincide for all participants
	Moderate risk	Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow-up and start of intervention do not coincide for all participants, but the proportion of participants for which this was the case was too low to induce important bias; the authors used appropriate methods to adjust for the selection bias; or the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.
	Serious risk	Selection into the study was related to intervention and outcome; or Start of follow-up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time.
	Critical risk	Selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time.
	No information	No information is reported about selection of participants into the study or whether start of follow-up and start of intervention coincide
Bias in measurement of interventions	**Low risk**	Intervention status is well defined and based solely on information collected at the time of intervention
	Moderate risk	Intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively
	Serious risk	Intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome
	Critical risk	(Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases

(Continued)

	No information	No definition of intervention or no explanation of the source of information about intervention status
Bias due to departures from intended interventions	**Low risk**	No bias due to departure from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued
	Moderate risk	Bias due to departure from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) departures from intended intervention reflect the natural course of events after initiation of intervention.
	Serious risk	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.
	Critical risk	Substantial departures from the intended intervention are present and are not adjusted for in the analysis**.**
	No information	No information is reported on whether there is departure from the intended intervention.
Bias due to missing data	**Low risk**	Data were reasonably complete; or Proportions and reasons of missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias.
	Moderate risk	Proportions of missing participants differ across interventions or reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis.
	Serious risk	Proportions of missing participants differ substantially across interventions or reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.
	Critical risk	(Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.

(Continued)

	No information	No information is reported about missing data or the potential for data to be missing
Bias in measurement of outcomes	**Low risk**	The methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status.
	Moderate risk	The methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status.
	Serious risk	The methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status.
	Critical risk	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.
	No information	No information is reported about the methods of outcome assessment.
Bias in selection of the reported result	**Low risk**	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.
	Moderate risk	The outcome measurements and analyses are consistent with an a priori plan; or are clearly defined, and internally and externally consistent; and

(Continued)

		There is no indication of selection of the reported analysis from among multiple analyses; and There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
	Serious risk	Outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.
	Critical risk	There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results.
	No information	There is too little information to make a judgment, for example if only an abstract is available for the study.
Overall judgment about risk of bias	**Low risk**	The study is judged to be at low risk of bias for all domains.
	Moderate risk	The study is judged to be at low or moderate risk of bias for all domains.
	Serious risk	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.
	Critical risk	The study is judged to be at critical risk of bias in at least one domain.
	No information	There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgment is required for this).

HISTORY

Protocol first published: Issue 1, 2016
Review first published: Issue 9, 2017

Date	Event	Description
20 January 2016	Amended	External source of support added

CONTRIBUTIONS OF AUTHORS

Lucy Platt led the writing of the protocol, the screening of papers, data extraction, analyses and write-up of the review.

Silvia Minozzi contributed to prepare the protocol, assessed risk of bias of the included studies and contributed to writing the text of the review.

Jennifer Reed contributed to the literature search, 'Risk of bias' assessment and data extraction.

Peter Vickerman contributed to the development of the protocol, interpretation of findings and the write-up of text of the review.

Holly Hagan contributed to the 'Risk of bias' assessment, the analysis plan and interpretation of findings and the write-up of review text.

Clare French led on the 'Risk of bias' assessment.

Ashly Jordan contributed to the risk of bias assessment and interpretation of findings.

Louisa Degenhardt contributed to the development of the protocol as well as the write-up of the review.

Vivian Hope contributed to the interpretation of findings and write-up of the review.

Sharon Hutchinson contributed to the interpretation of findings and write up of the review.

Lisa Maher contributed to the development of the protocol, the identification of unpublished data, the interpretation of findings and write-up of the review.

Norah Palmateer contributed to the development of the protocol and write-up of the review.

Avril Taylor contributed to the development of the protocol and write-up of the review.

Julie Bruneau contributed to the identification of unpublished data and the write-up of the review.

Matthew Hickman contributed to the development of the protocol, interpretation of findings and the write-up of text of the review.

DECLARATIONS OF INTEREST

Lucy Platt: none known.

Jennifer Reed: none known.

Silvia Minozzi: none known.

Peter Vickerman: received research grant funding off Gilead for doing work unrelated to this project.

Holly Hagan: none known.

Clare French: none known.

Ashly Jordan: none known.

Louisa Degenhardt: I have received untied educational grants from Reckitt Benckiser for the postmarketing surveillance of buprenorphine-naloxone tablets and soluble film (2006 to 2013), the development of an opioid-related behaviour scale (2010), and from Mundipharma for the conduct of postmarketing surveillance studies following the introduction of a new formulation of oxycodone in Australia. All such studies' design, conduct and interpretation of findings are the work of the investigators; the funders had no role in these. They had no knowledge of this work.

Vivian Hope: none known.

Sharon Hutchinson: outside the submitted work, received honoraria from pharma (Abbvie and Gilead) for speaking at conferences/ meetings on the epidemiology and treatment of HCV infection.

Lisa Maher: none known.

Norah Palmateer: none known.

Avril Taylor: the Scottish Government funded the Needle Exchange Surveillance Initiative. Some of the data from this is used in the paper under consideration.

Julie Bruneau: outside the submitted work, received honoraria from pharma (Merck and Gilead) as advisor on the treatment of HCV infection among people who inject drugs.

Matthew Hickman: none known.

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- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added a final review author, Prof Julie Bruneau, who contributed some of the unpublished data and advised on the review analyses and write-up.

We have changed the title to refer to opioids instead of opiates. Opioid encompasses synthetic opiates as well as those derived from opium, whereas opiates just include drugs derived from opium.

We added in another control intervention that included low coverage of NSP. This became necessary as it was clear following data extraction that many comparisons were made against this intervention exposure.

We also added to the description of the 'Risk of bias' assessment following its application. When the protocol was first published the tool was being piloted, and it was updated during the course of the review. We adapted our protocol to reflect these changes. We also added in additional confounders to be extracted from the protocol, since after extracting the first few papers it became clear that we had omitted relevant confounders.

We updated our approach to dealing with measures of treatment effect to reflect the dominant effect estimates that we were extracting. We treated odds ratios as an approximation of the risk ratio despite the variation in HCV incidence. We checked the legitimacy of this approach in a sensitivity analysis, excluding studies reporting odds ratios only.

We excluded studies where data regarding drug treatment or NSP were missing or unavailable from the analysis but not the review. We updated the review to clarify this point.

The subgroup analysis differed from that specified in the review protocol since there was insufficient information to assess impact by type of NSP, frequency of injecting, dose of OST, duration or age, ethnicity of participants. We did not assess impact by recruitment site of participants either since most studies recruited across multiple sites and methods, making it difficult to clearly differentiate methods.

The sensitivity analysis differed from that specified in the protocol in several ways. We did not exclude studies that reported incident rate ratios as effect estimates, since only a few studies used incident rate ratios. Instead we removed estimates derived from unpublished datasets as part of our sensitivity analyses since more estimates were derived in this way, making them a more substantive part of the analysis. The original protocol also stated that we would exclude studies that only assessed the impact of the intervention at baseline. We did this in the review but changed the wording to say that we excluded studies that used odds ratios as effect estimates and were cross-sectional in design. This is the same as excluding baseline measures only, but we wanted to more clearly specify that the sensitivity analysis had explored the effect of pooling different study designs.

INDEX TERMS

Medical Subject Headings (MeSH)

*Needle-Exchange Programs; *Opiate Substitution Treatment [methods]; Hepatitis C [epidemiology] [*prevention & control] [transmission]; Program Evaluation; Substance Abuse, Intravenous [*complications]

MeSH check words

Female; Humans; Male